

Hypnotics and Anxiolytics: Field and laboratory measures of drug safety in driving performance and cognitive functions

Citation for published version (APA):

Leufkens, T. R. M. (2009). *Hypnotics and Anxiolytics: Field and laboratory measures of drug safety in driving performance and cognitive functions*. [Doctoral Thesis, Maastricht University]. Maastricht University. <https://doi.org/10.26481/dis.20091009tl>

Document status and date:

Published: 01/01/2009

DOI:

[10.26481/dis.20091009tl](https://doi.org/10.26481/dis.20091009tl)

Document Version:

Publisher's PDF, also known as Version of record

Please check the document version of this publication:

- A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher's website.
- The final author version and the galley proof are versions of the publication after peer review.
- The final published version features the final layout of the paper including the volume, issue and page numbers.

[Link to publication](#)

General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal.

If the publication is distributed under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license above, please follow below link for the End User Agreement:

www.umlib.nl/taverne-license

Take down policy

If you believe that this document breaches copyright please contact us at:

repository@maastrichtuniversity.nl

providing details and we will investigate your claim.

HYPNOTICS AND ANXIOLYTICS

Field and laboratory measures of drug safety in driving
performance and cognitive functions

COLOPHON

© T.R.M. Leufkens, Maastricht, 2009

ISBN 978-90-9024605-5

Hypnotics and anxiolytics: Field and laboratory measures of drug safety in driving performance and cognitive functions

Thesis with summary in English and Dutch

Cover design: YDVormgever.nl | Sanne Stockbroekx

Photography: YDVormgever.nl

Typesetting and layout: Tim R.M. Leufkens

Printing: Ipskamp Drukkers, Enschede, The Netherlands

HYPNOTICS AND ANXIOLYTICS

Field and laboratory measures of drug safety in driving
performance and cognitive functions

PROEFSCHRIFT

*ter verkrijging van de graad van doctor aan de Universiteit Maastricht, op gezag
van de Rector Magnificus, Prof. mr. G.P.M.F. Mols, volgens het besluit van het
College van Decanen, in het openbaar te verdedigen op vrijdag 9 oktober 2009
om 10:00 uur*

door

Tim R.M. Leufkens

Geboren op 17 maart 1978 te Berg aan de Maas

Promotor

Prof. dr. W.J. Riedel

Copromotor

Dr. A. Vermeeren

Beoordelingscommissie

Prof. dr. H.L.G.J. Merckelbach (voorzitter)

Dr. A. Blokland

Prof. dr. W.H. Brouwer (Rijksuniversiteit Groningen)

Dr. E.J.W. van Someren (Vrije Universiteit Amsterdam)

Prof. dr. F.R.J. Verhey

The research described in this dissertation was conducted at the Department of Neuropsychology and Psychopharmacology, Maastricht University, The Netherlands. The studies were funded by H. Lundbeck A/S, Copenhagen, Denmark (*chapter 1*), Pfizer Inc., New York, USA (*chapter 6*) and by the integrated project Driving Under the Influence of Drugs, Alcohol and Medicines (DRUID), which is part of the European Union's 6th Framework Programme (*chapters 4 and 5*). The chapters 4 and 5 reflect only the author's view. The European Community is not liable for any use that may be made of the information contained therein.

The studies in this dissertation are based on data collected in five studies. In the study described in *chapter 1* data were collected from 25 healthy, younger volunteers. The study described in *chapter 2* included 18 healthy, elderly volunteers. In the first study with insomnia patients (*chapter 4*), a total of 42 patients and 21 healthy, elderly volunteers were included. In the subsequent study (*chapter 5*) data were collected from 32 insomnia patients and 16 healthy, elderly subjects. The study described in *chapter 6* included 18 healthy, younger subjects.

Publication of this thesis is financially supported by H. Lundbeck A/S, Denmark, the Dutch Ministry of Transport, Public Works and Water Management (Ministerie van Verkeer en Waterstaat), the Dutch Sleep Wake Organization (Nederlandse Slaap Waak Organisatie; NSWO) and Abbott BV, The Netherlands.

Contents

General Introduction	7
Chapter 1 Highway driving performance and cognitive functioning the morning after bedtime and middle-of-the-night use of gaboxadol, zopiclone and zolpidem	21
Chapter 2 Highway driving in elderly the morning after bedtime use of hypnotics: a comparison between temazepam 20 mg, zopiclone 7.5 mg and placebo	49
Chapter 3 Zopiclone's residual effects on actual driving performance in a standardized test: a pooled analysis of age and gender effects in four placebo controlled studies	73
Chapter 4 On-the-road driving performance and driving related skills in untreated insomnia patients and chronic users of hypnotics	97
Chapter 5 Residual effects of zopiclone 7.5 mg on highway driving performance in elderly insomnia patients: a placebo controlled study	131
Chapter 6 Cognitive, psychomotor and actual driving performance in healthy volunteers after immediate and extended release formulations of alprazolam 1 mg	155
Chapter 7 General Discussion	177
Summary	191

Samenvatting	199
Dankwoord	207
Curriculum Vitae	211
Publications	213

GENERAL INTRODUCTION

GENERAL INTRODUCTION

In 2004, the World Health Organization (WHO) raised the alarm by reporting that worldwide nearly 1.2 million people are killed and 50 million become injured in road traffic accidents each year (WHO, 2004). According to the same report, one of the risk factors influencing crash involvement is the use of medicinal drugs and in particular the so-called 'psychoactive drugs'.

Psychoactive medicinal drugs act primarily on the central nervous system and are widely used for the treatment of a variety of psychiatric and neurological problems. Due to their neuronal mechanism of action, they are able to alter mood and behavior and, ideally, these alterations are exclusively therapeutic. However, frequently these drugs also produce undesirable side effects that manifest themselves mainly in deterioration of mental and behavioral functions. For instance, memory, attention and motor responses can be impaired as a result of sedative side effects. This impairment may then have serious consequences for the performance and safety of daily activities, such as participation in road traffic. Driving performance, as it is a combination of simultaneously executed cognitive and psychomotor skills, can be significantly impaired after use of psychoactive medication. Consequently, driving under the influence of psychoactive medicinal drugs may lead to hazardous and even fatal situations.

Hypnotics and anxiolytics

Among the most frequently prescribed psychoactive medicinal drugs are hypnotics and anxiolytics, for the treatment of insomnia and anxiety disorders, respectively. The focus in this dissertation is on GABAergic hypnotics and anxiolytics, but nowadays antidepressant drugs, modifying monoaminergic neurotransmitter systems, are prescribed as hypnotic or anxiolytic treatment as well. The most frequently used GABAergic hypnotics and anxiolytics are benzodiazepines, such as oxazepam, diazepam and temazepam. Other GABAergic hypnotics are the so-called 'Z-drugs' (zopiclone, zolpidem and zaleplon) which have become increasingly preferable in the treatment of insomnia because of their beneficial safety profile (Siriwardena et al., 2006).

GABAergic hypnotics and anxiolytics act primarily on GABA_A receptors by facilitating the binding of the neurotransmitter GABA to its receptor. GABA is the most abundant inhibitory neurotransmitter in the brain and plays an important role in modulating activity of neurons throughout the whole brain. Binding of GABA to its receptor causes chloride channels in the neuronal membrane to open, creating an influx of negatively charged chloride into the neuron. This causes hyperpolarization of the neuron and decreases therewith its activity. GABAergic hypnotics and anxiolytics enhance the action of GABA which will lead to an even more reduced activity of the neurons.

GABA_A receptors are composed of several subunits which can be classified into α (1-6), β (1-3), γ (1-3), δ , ϵ , θ , π and ρ (1-3) subunit classes (Rudolph and Mohler, 2006). Depending on their composition they play a role in different kinds of behavior. It has been shown that the sleep-inducing effect of GABAergic drugs is mediated by GABA_A receptors containing the α 1 subunit, whereas the α 2-containing GABA_A receptor is responsible for the anxiolytic action of GABAergic drugs (Korpi and Sinkkonen, 2006).

Besides therapeutic effects, hypnotics and anxiolytics often produce side-effects or residual effects. Adverse effects associated with the use of anxiolytics are daytime drowsiness, dizziness and sedation. A major problem of hypnotics is residual sedation the morning after evening- or middle-of-the-night administration. The side effects of hypnotics and anxiolytics are expressed in a common mode. They impair cognitive and psychomotor functions and negatively affect performance in a variety of tasks, such as driving. To date, the impairing effects on driving of hypnotics and anxiolytics have been widely established in a large number of experimental studies (cf. Vermeeren, 2004). From these studies it has become clear that the severity of effects on driving depends on a variety of factors, such as the drug's half-life and the prescribed dose.

Limitations of previous studies

Despite the vast amount of existing data concerning the effects of hypnotics and anxiolytics on driving, a number of questions still have remained unanswered.

GENERAL INTRODUCTION

Experimental studies investigating the effects of hypnotics and anxiolytics have been mainly conducted with healthy young volunteers. These studies have yielded substantial information of the impairing effects of hypnotics and anxiolytics independent of their efficacy. However, it is often argued whether the subject sample can be considered representative for the target population of the drugs, i.e. patients suffering from anxiety disorders or insomnia. Responses to the adverse effects may be different in patients than in healthy young volunteers because of the underlying disorder in patients. For example, efficacious hypnotics without residual effects are expected to improve daytime performance in insomniac patients. In contrast, healthy subjects do not benefit from the sleep-inducing effects of hypnotics as compared to insomniac patients and may not show any improvement in performance. It is, therefore, necessary to assess how and to what extent the effects of medicinal drugs interact with the disorder of the patient.

A second limitation associated with the inclusion of healthy volunteers in experimental studies is that they are medication naïve, whereas patients often have been using hypnotics and anxiolytics for prolonged periods (Curran et al., 2003). Chronic use may result in the development of tolerance to the impairing effects of these drugs. Epidemiological studies have shown, however, that there is still a significantly increased risk of crash involvement after one month of treatment, suggesting that tolerance is never complete (Neutel, 1998). These results have been confirmed for the anxiolytics drugs in an experimental study by van Laar and associates (1992), but the impairing effects of hypnotics in chronic users have not yet been investigated.

Thirdly, as is especially the case for hypnotics, the majority of GABAergic drugs are prescribed to older patients (Drake et al., 2003, Glass et al., 2005, Kamel and Gammack, 2006). Yet, there is a lack of data concerning the effects of anxiolytics and hypnotics on driving in elderly. In 1995, Vermeeren and De Gier were commissioned by the National Swedish Road Safety Office and The Netherlands' Ministry of Transport and Public Works to develop a consensus of methodological guidelines for experimental research on medicinal drugs affecting driving performance. Their consultation of international experts in the

field of drugs and driving yielded a set of recommendations for sound experimental research. One of the guidelines was that studies need to be conducted with subjects across the whole age range of active drivers. With age, physical changes may arise, such as a reduction in liver capacity and lean body mass, which may result in a prolonged elimination half-life of medicinal psychoactive drugs in elderly as compared to younger volunteers. Additionally, with age, sensitivity to the adverse effects may be increased (Woodward, 1999). Therefore, effects of drugs need to be assessed in different age groups.

Besides a lack of studies conducted with elderly, Vermeeren and De Gier (1995) reported that until then the majority of studies were undertaken with male volunteers. Insomnia and anxiety disorders are most prevalent in women, however (Bekker and Van Mens-Verhulst, 2007, Morin et al., 2006) and parallel to that, use of hypnotics and anxiolytics is more prevailing in women than in men (Morlock et al., 2006). In addition, medicinal drugs can produce different pharmacological responses in females than in males, mainly caused by differences in volume of distribution, but sometimes also by both pharmacokinetic and pharmacodynamic gender differences (Anderson, 2008, Schwartz, 2003). Therefore, driving performance after administration of anxiolytics or hypnotics may be differently affected between males and females. Despite the growing number of studies comprising gender balanced samples, it is still not clear whether this is the case. The majority of those studies have been conducted according to within subject designs with relatively small sample sizes. As a consequence, comparisons of drug effects on performance between females and males are not justified in terms of statistical power. In order to provide robust evidence concerning gender differences in drug effects on performance sample sizes should be increased considerably. An obvious approach for achieving a large sample size is to design a study with a sufficient number of participants. Yet, if studies already exist that are conducted with similar standardized procedures, it is possible to pool their raw data. Therewith, a larger study sample is created allowing comparing drug effects between females and males.

GENERAL INTRODUCTION

Finally, results of experimental studies on existing drugs provide new insights concerning their influence on driving and may lead to the development of new improved medicinal drugs with regard to their side-effects. For example, the anxiolytic benzodiazepine alprazolam was shown to produce severe impairment on driving one hour after administration of its therapeutically prescribed dose of 1 mg (Verster et al., 2002b). In order to reduce the adverse events associated with the rapid distribution of alprazolam 1 mg in the circulatory system, the compound was changed in an extended release formulation. Performance on cognitive and psychomotor tasks appeared to be less impaired after the extended release formulation as compared to its original compound (Busto et al., 2000, Mumford et al., 1995, Rickels, 2004). It remains to be investigated, however, to what extent manipulations of formulations change the magnitude of impairment on driving performance.

Aim of this dissertation

The aim of this dissertation is to evaluate to what extent the effects of hypnotics and anxiolytics on driving performance are modulated by factors, such as age, gender, disorder or drug formulation. It is still not clear whether the results of experimental studies conducted with healthy young volunteers translate to therapeutic use in patients. Therefore, the effects of hypnotics on driving performance are investigated in a stepwise manner. Four experimental studies are presented following similar designs and procedures, but differing in sample composition. In the first study, driving performance after administration of hypnotics is assessed in healthy young volunteers. Next, a study is conducted with similar methodology, but investigating the effects of hypnotics in healthy older drivers. As a third step, the effects of untreated insomnia and chronic use of hypnotics are studied, comparing driving performance between insomnia patients not or infrequently using hypnotics, insomnia patients chronically using hypnotics and healthy, age matched, good sleepers. Lastly, driving performance is evaluated after administration of a frequently prescribed hypnotic in insomnia patients not or infrequently using hypnotics, insomnia patients chronically using hypnotics and healthy, age matched, good sleepers. Furthermore, a pooled

analysis is presented providing more insight into the impairing effects of the most frequently prescribed non-benzodiazepine zopiclone. Finally, an experimental study is presented comparing the effects of different formulations of a frequently prescribed anxiolytic.

Methodology

All experimental studies presented in this dissertation used the same standardized highway driving test developed by O'Hanlon in the early 1980's (O'Hanlon, 1984). In this test the subject operates a specially instrumented vehicle over a 100 km (61 mi) primary highway circuit, accompanied by a licensed driving instructor having access to dual controls. The subject's task is to maintain a constant speed of 95 km/h (58 mi/h) and a steady lateral position between the delineated boundaries of the slower traffic lane. The vehicle speed and lateral position are continuously recorded. After the subject completes the circuit in about 1 hour, these signals are edited off line to remove data recorded during overtaking maneuvers or disturbances caused by roadway or traffic situations. The remaining data are then used to calculate means and standard deviations of lateral position and speed. The pooled lateral position variance is calculated, and its square root, the mean-adjusted standard deviation of lateral position (SDLP in centimeters) is taken as the primary outcome variable. SDLP is an integrated measure of road tracking error or "weaving". SDLP is an extremely reliable index (test-retest $r = 0.70$ to 0.90) of individual driving performance and has proven to be sensitive to many sedating drugs (O'Hanlon and Ramaekers, 1995, O'Hanlon et al., 1995, Ramaekers, 2003, Vermeeren et al., 1995a, Vermeeren et al., 1995b, Vermeeren et al., 1998, Vermeeren et al., 2002, Verster et al., 2002a, Verster et al., 2002b). The secondary outcome variable is the standard deviation of speed (SDSP in km/h). The SDSP is an index of the ability to maintain a constant speed. The general hypothesis in this dissertation was that evening administration of hypnotics produces residual detrimental effects on driving performance in the morning after. Due to dosage and elimination half-life, sufficient concentrations to produce impairment may still be present in the brain at this time. Therefore, all studies hypothesize

increased SDLP after hypnotic use compared to placebo, except when specified otherwise.

Outline of this dissertation

Chapter 1 describes a study investigating the effects of hypnotics on driving performance in a total of 25 younger, healthy volunteers. They are administered evening and middle-of-the-night administration of gaboxadol 15 mg and placebo, evening administration of zopiclone 7.5 mg and middle-of-the-night administration of zolpidem 10 mg. Gaboxadol is a newly developed hypnotic. Results from clinical trials suggest that gaboxadol does not produce significant residual sedation after bedtime doses of 15 mg. Based on previous studies (Vermeeren et al., 1998, 2002, Verster et al., 2002a) evening doses of zopiclone 7.5 mg and middle-of-the-night doses of zolpidem 10 mg are expected to have residual sedating effects the next morning that are associated with moderately to severe impairing effects on driving and cognitive functioning. These drugs are included as active controls to demonstrate sensitivity of the tests and procedures used in this study. Effects of zopiclone 7.5 mg presented in this chapter serve as a reference to which results of *chapters 2, 4 and 5* will be compared.

Chapter 2 presents a study investigating whether the effects on driving performance the morning after evening administration of hypnotics are more pronounced in elderly drivers. It is hypothesized that, due to age-related physical changes, elderly may be more sensitive to the residual effects of hypnotics. In the study, performance on the highway driving test is compared after administration of temazepam 20 mg, zopiclone 7.5 mg and placebo in 18 healthy elderly drivers.

In *chapter 3*, results of the studies described in *chapters 1 and 2* are pooled together with another two previous studies using similar designs and procedures (Vermeeren et al., 1998, Vermeeren et al., 2002). Data of the driving test following evening administration of the zopiclone 7.5 mg and placebo are analyzed in order to provide more and robust insight into the impairing effects of zopiclone 7.5 mg on driving performance. It is hypothesized

that driving after zopiclone 7.5 mg is differently impaired between male and female subjects. Therefore, one main objective of the study is to determine whether the effects of zopiclone 7.5 mg are modified by gender.

Chapter 4 and 5 present studies comparing driving performance between insomnia patients chronically using hypnotics, insomnia patients infrequently using hypnotics and healthy, age matched, good sleepers. *Chapter 4* explores the effect of insomnia and chronic use of hypnotics on driving performance without an experimental, pharmacological intervention. The insomnia patients chronically using hypnotics ingested their own prescribed medication at bedtime and the other two groups did not ingest any hypnotics.

In *chapter 5* the question whether the effects of hypnotics on driving performance are modulated by insomnia and chronic use of hypnotics is investigated. It is hypothesized that insomnia may attenuate the residual effects of hypnotics due to the underlying disorder. In addition, it is hypothesized that chronic use may even more attenuate the residual effects of hypnotics due to the development of tolerance. The chapter presents a double blind, placebo controlled, crossover study comparing the effects of zopiclone 7.5 mg on driving performance the morning after evening administration between insomniac patients chronically using hypnotics, insomniac patients infrequently using hypnotics and healthy, age matched, good sleepers.

In *chapter 6* it is investigated to what extent an extended release formulation of a benzodiazepine anxiolytic reduces the impairing effects on driving performance as compared to its immediate release equivalent. It is hypothesized that driving impairment would be less pronounced after administration of the extended release formulation than the immediate release formulation, due to differences in the pharmacokinetic profile of the formulations. The study presented in the chapter assesses driving performance after administration of immediate and extended release formulations of alprazolam 1 mg and placebo in 18 healthy younger volunteers.

Finally, in *chapter 7* the results from the previous chapters are summarized and discussed. Additionally, suggestions for further research are proposed.

REFERENCES

- Anderson, G. D. Gender differences in pharmacological response. *Internat Rev Neurobiol*, 2008, 83: 1-10.
- Bekker, M. H. J. & Van Mens-Verhulst, J. Anxiety disorders: Sex differences in prevalence, degree, and background, but gender-neutral treatment. *Gen Med*, 2007, 4: S178-S193.
- Busto, U. E., Kaplan, H. L., Wright, C. E., Gomez Mancilla, B., Zawertailo, L., Greenblatt, D. J. & Sellers, E. M. A comparative pharmacokinetic and dynamic evaluation of alprazolam sustained-release, bromazepam, and lorazepam. *J Clin Psychopharmacol*, 2000, 20: 628-635.
- Curran, H. V., Collins, R., Fletcher, S., Kee, S. C., Woods, B. & Iliffe, S. Older adults and withdrawal from benzodiazepine hypnotics in general practice: effects on cognitive function, sleep, mood and quality of life. *Psychol Med*, 2003, 33: 1223-1237.
- Drake, C. L., Roehrs, T. & Roth, T. Insomnia causes, consequences, and therapeutics: an overview. *Depress Anxiety*, 2003, 18: 163-176.
- Glass, J., Lanctot, K. L., Herrmann, N., Sproule, B. A. & Busto, U. E. Sedative hypnotics in older people with insomnia: meta-analysis of risks and benefits. *BMJ Clin Res*, 2005, 331: 1169-1175.
- Kamel, N. S. & Gammack, J. K. Insomnia in the elderly: cause, approach, and treatment. *Am J Med*, 2006, 119: 463-469.
- Korpi, E. R. & Sinkkonen, S. T. GABA(A) receptor subtypes as targets for neuropsychiatric drug development. *Pharmacol Ther*, 2006, 109: 12-32.
- Morin, C. M., Leblanc, M., Daley, M., Gregoire, J. P. & Merette, C. Epidemiology of insomnia: Prevalence, self-help treatments, consultations, and determinants of help-seeking behaviors. *Sleep Med*, 2006, 7: 123-130.
- Morlock, R. J., Tan, M. & Mitchell, D. Y. Patient characteristics and patterns of drug use for sleep complaints in the United States: analysis of National Ambulatory Medical Survey data, 1997-2002. *Clin Ther*, 2006, 28: 1044-1053.

- Mumford, G. K., Evans, S. M., Fleishaker, J. C. & Griffiths, R. R. Alprazolam absorption kinetics affects abuse liability. *Clin Pharmacol Ther*, 1995, 57: 356-365.
- Neutel, I. Benzodiazepine-related traffic accidents in young and elderly drivers. *Hum Psychopharmacol Clin Exp*, 1998, 13: S115-S123.
- O'Hanlon, J. F. Driving performance under the influence of drugs: rationale for, and application of, a new test. *Br J Clin Pharmacol*, 1984, 18 Suppl 1: 121s-129s.
- O'Hanlon, J. F. & Ramaekers, J. G. Antihistamine effects on actual driving performance in a standard test: a summary of Dutch experience, 1989-94. *Allergy*, 1995, 50: 234-242.
- O'Hanlon, J. F., Vermeeren, A., Uiterwijk, M. M., Van Veggel, L. M. & Swijgman, H. F. Anxiolytics' effects on the actual driving performance of patients and healthy volunteers in a standardized test. An integration of three studies. *Neuropsychobiol*, 1995, 31: 81-88.
- Ramaekers, J. G. Antidepressants and driver impairment: empirical evidence from a standard on-the-road test. *J Clin Psychiat*, 2003, 64: 20-29.
- Rickels, K. Alprazolam extended-release in panic disorder. *Exp Opin Pharmacother*, 2004, 5: 1599-1611.
- Rudolph, U. & Mohler, H. GABA-based therapeutic approaches: GABAA receptor subtype functions. *Curr Opin Pharmacol*, 2006, 6: 18-23.
- Schwartz, J. B. The influence of sex on pharmacokinetics. *Clin Pharmacokinet*, 2003, 42: 107-121.
- Siriwardena, A. N., Qureshi, Z., Gibson, S., Collier, S. & Latham, M. GPs' attitudes to benzodiazepine and 'Z-drug' prescribing: a barrier to implementation of evidence and guidance on hypnotics. *Br J Gen Pract*, 2006, 56: 964-967.
- Van Laar, M. W., Volkerts, E. R. & Van Willigenburg, A. P. Therapeutic effects and effects on actual driving performance of chronically administered buspirone and diazepam in anxious outpatients. *J Clin Psychopharmacol*, 1992, 12: 86-95.

GENERAL INTRODUCTION

- Vermeeren, A. Residual effects of hypnotics: epidemiology and clinical implications. *CNS Drugs*, 2004, 18: 297-328.
- Vermeeren, A., Danjou, P. E. & O'Hanlon, J. F. Residual effects of evening and middle-of-the-night administration of zaleplon 10 and 20 mg on memory and actual driving performance. *Hum Psychopharmacol*, 1998, 13: S98-S107.
- Vermeeren, A. & De Gier, J. J. Methodological guidelines for experimental research in Drugs and Driving: accomplishments and future needs. In Krueger, H.-P., Kohnen, R. & Schoch, H. (Eds.) *Medicamente in Strassenverkehr: Auftreten, Risiken Konsequenzen*. Stuttgart, Gustav Fisher Verlag, 1995.
- Vermeeren, A., Jackson, J. L., Muntjewerff, N. D., Quint, P. J., Harrison, E. M. & O'Hanlon, J. F. Comparison of acute alprazolam (0.25, 0.50 and 1.0 mg) effects versus those of lorazepam 2 mg and placebo on memory in healthy volunteers using laboratory and telephone tests. *Psychopharmacol*, 1995a, 118: 1-9.
- Vermeeren, A., O'Hanlon, J. F., Declerck, A. C., & Kho, L. Acute effects of zolpidem and flunitrazepam on sleep, memory and driving performance, compared to those of partial sleep deprivation and placebo. *Acta Thera*, 1995b, 21: 47-64.
- Vermeeren, A., Riedel, W. J., Van Boxtel, M. P., Darwish, M., Paty, I. & Patat, A. Differential residual effects of zaleplon and zopiclone on actual driving: a comparison with a low dose of alcohol. *Sleep*, 2002, 25: 224-231.
- Verster, J. C., Volkerts, E. R., Schreuder, A. H., Eijken, E. J., Van Heuckelum, J. H., Veldhuijzen, D. S., Verbaten, M. N., Paty, I., Darwish, M., Danjou, P. & Patat, A. Residual effects of middle-of-the-night administration of zaleplon and zolpidem on driving ability, memory functions, and psychomotor performance. *J Clin Psychopharmacol*, 2002a, 22: 576-583.
- Verster, J. C., Volkerts, E. R. & Verbaten, M. N. Effects of alprazolam on driving ability, memory functioning and psychomotor performance: a

randomized, placebo-controlled study. *Neuropsychopharmacol*, 2002b, 27: 260-269.

WHO. World report on road traffic injury prevention. In Peden, M., Scurfield, R., Sleet, D., Mohan, D., Hyder, A. A., Jarawan, E. & Mathers, C. (Eds.) Geneva, World Health Organization (WHO), 2004.

Woodward, M. Hypnosedatives in the elderly. *CNS Drugs*, 1999, 11: 263-279.

GENERAL INTRODUCTION

CHAPTER 1

Highway driving performance and cognitive functioning the morning after bedtime and middle-of-the-night use of gaboxadol, zopiclone and zolpidem

Accepted for publication as:

Leufkens TRM, Lund JS, Vermeeren A. Highway driving performance and cognitive functioning the morning after bedtime and middle-of-the-night use of gaboxadol, zopiclone and zolpidem. *Journal of Sleep Research*.

ABSTRACT

Gaboxadol is a selective extrasynaptic GABA_A receptor agonist previously in development for the treatment of insomnia. Due to its short half-life (1.5-2 hrs) it is expected to be free from residual effects the next morning. The present study assessed the residual effects of evening and middle-of-night administration of gaboxadol 15 mg on cognitive, psychomotor and driving performance. Twenty-eight healthy volunteers entered the study with 25 (12 women; mean age 31.4 years) completing a double-blind, placebo-controlled, active-referenced five-way cross over study. Each treatment night subjects ingested one capsule at 11:00 PM and one at 4:00 AM. Treatments were placebo at both times, gaboxadol 15 mg or zopiclone 7.5 mg followed by placebo, and placebo followed by gaboxadol 15 mg or zolpidem 10 mg. Effects on cognition and psychomotor performance were assessed between 7:30-8:30 AM, and on driving between 9:00-10:00 AM. Driving, as measured by standard deviation of lateral position in an on-the-road driving test, was nearly significantly ($p<0.07$) impaired after evening administration of gaboxadol for the all-subjects-completed-set ($n=25$), but significantly ($p<0.05$) in the full-analysis-set ($n=28$). Effects of all other active treatments on driving were significant. Evening administration of gaboxadol had minor effects on divided attention only, whereas middle-of-the-night administration significantly impaired performance in all tests except memory. Zolpidem and zopiclone significantly impaired performance in every test except tracking after zopiclone. Gaboxadol 15 mg can produce minor residual effects on driving after evening administration. Administration later at night is associated with moderately impairing residual effects on driving and psychomotor performance, but not on memory.

INTRODUCTION

Residual daytime sleepiness and impairment of psychomotor and cognitive functioning the day after bedtime administration is one of the main problems associated with the use of hypnotics (Vermeeren, 2004). This poses a crucial

problem for users of hypnotics who must operate vehicles. Epidemiological studies have shown that the use of benzodiazepine hypnotics, as well as zopiclone, is associated with increased risk of injurious car accidents (Barbone et al., 1998). In general, risks increase with dose and elimination half-life (Neutel, 1998).

Gaboxadol (4, 5, 6, 7-tetrahydroisoxazolo [5, 4-c] pyridin-3-ol, THIP) is a selective extrasynaptic GABA_A receptor agonist previously in development for the treatment of insomnia. It has a relatively high affinity for benzodiazepine-insensitive, $\alpha_4\beta_3\delta$ -, and $\alpha_6\beta_3\delta$ -containing GABA_A receptors which are located extrasynaptically and seem to be involved in tonic GABAergic inhibition (Ebert et al., 2006, Lundahl et al., 2006, Storustovu and Ebert, 2006). Clinical studies (Faulhaber et al., 1997, Lancel et al., 2001, Mathias et al., 2001, Deacon et al., 2005, Mathias et al., 2005, Deacon et al., 2007, Walsh et al., 2007) have shown that gaboxadol in doses between 5 and 20 mg significantly and dose dependently improves subjective and objective measures of sleep. It was found to decrease sleep latencies and to increase total sleep time in healthy young and elderly volunteers, and in patients with insomnia. The most frequently reported adverse events after a dose of gaboxadol 15 mg were dizziness, abdominal pain, nausea, vomiting and dysmenorrhoea.

Most important with respect to gaboxadol's potential to produce residual effects is that pharmacokinetic studies have shown that the drug is rapidly absorbed and eliminated. Peak plasma concentrations were found approximately 30 minutes after oral administration (Schultz et al., 1981) and the average elimination half-life ranged between 1.5 and 2 hrs (Lund et al., 2005). The majority of gaboxadol is excreted unchanged and a glucuronide conjugate of gaboxadol is the only metabolite formed in significant amount (Lund et al., 2006). Gaboxadol's half-life falls between those of zaleplon (1 hr) and zolpidem (2.5 hrs), both hypnotics that have been shown unlikely to produce residual effects on driving the morning after bedtime administration of their recommended doses (Vermeeren et al., 1995, Vermeeren et al., 1998, Vermeeren et al., 2002, Vermeeren, 2004, Verster et al., 2002, Verster et al.,

2004). It may, therefore, be expected that residual effects after an evening dose of gaboxadol are absent the following morning.

Currently, three clinical trials have been published in which the residual effects of bedtime administration of gaboxadol were assessed and that support the expectations mentioned above (Mathias et al., 2005, Lundahl et al., 2006, Walsh et al., 2007). None of them found significant differences from placebo on cognitive functioning the next morning. A limitation of these studies is, however, that none of them included an adequate active control drug to demonstrate sensitivity of the procedures to detect residual effects on performance. Although zolpidem 10 mg is adequate for comparison of efficacies, it is unlikely to produce any residual effects more than 9 hrs after bedtime administration (cf. Vermeeren, 2004, Swainston Harrison and Keating, 2005). In addition, the tests used were all of short duration and none of them used tests which could be extrapolated to driving performance.

The primary objective of the present study was to evaluate the residual effects of single oral doses of gaboxadol 15 mg ingested at bedtime and in the middle-of-the-night on driving performance the next morning, using an on-the-road driving test. Effects were to be compared with those of placebo. A secondary objective was to compare these drugs' residual effects with those of placebo on memory and psychomotor functioning, and subjective alertness. Zopiclone 7.5 mg was selected as an active control for the bedtime dose of gaboxadol, because it was repeatedly found to have moderately impairing effects on driving the morning after bedtime administration (Vermeeren et al., 1998, Vermeeren et al., 2002). Zopiclone's effects on driving the morning after a middle-of-the-night dose are known to be severe, however (Vermeeren et al., 1998). Therefore, zolpidem 10 mg was selected as an active control for the middle-of-the-night dose of gaboxadol, because its effects on driving were previously found to be significant, but much milder than those of zopiclone after middle-of-the-night administration (Verster et al., 2002).

METHODS

Subjects

Twenty-eight healthy male and female volunteers (ages 22-44 years) without sleep complaints were recruited by means of advertisements in local newspapers. Volunteers were screened by a medical history questionnaire and physical examination. The latter included blood hematology and chemistry, urinalysis, drug and pregnancy tests, and a 12-lead electrocardiogram. For participation the following criteria had to be met: absence of any medical, endocrine, neurological or psychiatric condition, body mass index between 19 and 29 kg/m², normal vision (corrected or uncorrected), possession of a valid driving license for more than 3 years and average driving experience of at least 5000 km/year, and if female using an accepted method of contraception or surgically sterilized and not pregnant or breastfeeding.

Subjects were excluded by the following criteria: pregnant or breastfeeding, alcohol use of more than 21 or 14 alcohol containing beverages per week for men and women respectively, smoking more than 10 cigarettes per day, use of anxiolytics or antidepressants in the last 6 months, donation of blood or treatment with any investigational product within the last 3 months, use of any disallowed medicines or drugs of abuse within 2 weeks prior to first dosing.

During participation use of caffeine had to be less than 7 cups of coffee per day and was prohibited from 4 hrs prior to arrival on treatment days, until discharge the next morning. Alcohol intake was not allowed from 48 hours prior to each dosing until discharge. Smoking was prohibited from arrival until discharge and eating was not permitted from arrival until breakfast. Finally, subjects were required to abstain from strenuous exercise from 24 hours before dosing until discharge.

A total of 25 subjects (13 male, 12 female) completed the study. Their mean \pm SD age was 31.4 \pm 7.5 years and their mean \pm SD body mass index (BMI) was 23.3 \pm 2.5 kg/m². Two participants were withdrawn from the study after the third treatment period, and one after the fourth treatment period, due to protocol deviations.

CHAPTER 1

The study was conducted in accordance with the code of ethics on human experimentation established by the World Medical Association's Declaration of Helsinki (1964) and amended in Edinburgh (2000). The protocol was approved by the medical ethics committee of Maastricht University and University Hospital of Maastricht. Subjects were explained the aims, methods, and potential hazards of the study and they signed a written informed consent prior to any study-related assessments.

Design

The study was conducted according to a double-blind, five-way crossover design. Treatments were gaboxadol 15 mg administered in the evening, and middle-of-the-night, zopiclone 7.5 mg administered in the evening, zolpidem 10 mg administered in the middle-of-the-night, and placebo. Evening drug administration (23:00 hrs) was followed by placebo middle-of-the-night administration (04:00 hrs) and vice versa, or placebo at both times. Treatments were administered in identical looking capsules. Treatments were balanced over periods by randomly assigning 5 treatment sequences to the first 25 subjects.

Assessments

Residual effects were assessed using a highway driving test, a battery of laboratory tests measuring skills related to driving, memory and postural stability, and subjective rating scales. All of the tests have been previously found sensitive to the residual effects of hypnotics (Vermeeren et al., 1995, Vermeeren et al., 1998, Vermeeren et al., 2002, Vermeeren, 2004, Verster et al., 2002) and low doses of alcohol (Ramaekers et al., 1996, Vermeeren et al., 2002).

In the Standardized Highway Driving Test (O'Hanlon, 1984) the subject operates a specially instrumented vehicle over a 100 km (61 mi) primary highway circuit, accompanied by a licensed driving instructor having access to dual controls. The subject's task is to maintain a constant speed of 95 km/h (58 mi/h) and a steady lateral position between the delineated boundaries of the

slower traffic lane. The vehicle speed and lateral position are continuously recorded. These signals are edited off line to remove data recorded during overtaking maneuvers or disturbances caused by roadway or traffic situations. The remaining data are then used to calculate means and standard deviations of lateral position and speed. Standard deviation of lateral position (SDLP in centimeters) is the primary outcome variable. SDLP is a measure of road tracking error or “weaving”. The test duration is approximately 1 hour.

The Critical Tracking Test (CTT) measures the ability to control an unstable error signal in a first-order compensatory tracking task (Jex et al., 1966). Error is displayed as a horizontal deviation of a cursor from the midpoint on a horizontal, linear scale. Subjects use a joystick to null the error by returning the cursor to the midpoint. The frequency at which the subject loses the control is the critical frequency or lambda (λ_c) in rad/s. The final score is determined from the average of all but the lowest and the highest scores in five trials.

The Divided Attention Task measures the ability to divide attention between two simultaneously performed tasks (Moskowitz, 1973). In the primary task the subject performs the same tracking task described above, yet at a constant level of difficulty set at 50% of his or her maximum capacity. In the secondary task the subject monitors 24 peripheral displays in which single digits change asynchronously at 5-second intervals. Subjects are instructed to remove their foot from a pedal as rapidly as possible whenever the digit ‘2’ appears. This signal occurs twice at every location, in random order, at intervals of 5 to 25 sec. Tracking Error (in mm) and Average Reaction Time (in ms) are the respective performance measures.

The Digit Symbol Substitution Test (DSST) measures processing speed and working memory. It is a computerized version of the original paper and pencil test taken from the Wechsler Adults Intelligence Scale. The subject is briefly shown an encoding scheme consisting of a row of squares at the top of the screen, wherein nine digits are randomly associated with particular symbols. The same symbols are presented in a fixed sequence at the bottom of the screen as a row of separate response buttons. The encoding scheme and the response buttons remain visible while the subject is shown successive

CHAPTER 1

presentations of a single digit at the centre of the screen. The subject is required to match each digit with a symbol from the encoding list as rapidly as possible by clicking the corresponding response button, using the mouse. The number of digits correctly encoded within 3 minutes is the performance measure.

In the Word Learning Test (Rey, 1964), measuring verbal memory, a sequence of 15 monosyllabic nouns is shown on a computer display at a rate of one per two seconds. Immediately thereafter the subject is required to verbally recall as many words as possible. The sequence is repeated on four more trials, and the highest separate trial score is the Immediate Recall Score. After a delay of at least 30 minutes the subject is again required to recall as many words as possible without prompting. The total number of words correctly recalled is the Delayed Recall Score. Finally, the subject is shown a sequence of 30 words on the computer display, including 15 words from the original set and 15 new words in random order. The subject has to indicate as quickly as possible whether a word originates from the original set or not by pressing a corresponding buttons. The number and speed of correct responses are recorded as the Recognition Score and the Recognition Reaction Time (in ms), respectively.

Body Sway was measured using the stabilometry method of the International Society of Posturography (Kapteyn et al., 1983). The subjects stands on a force platform for 60 sec with the feet open at an angle of approximately 30°, first with their eyes open and fixed on a target 2 meters away, and then with their eyes closed. The system (Electropostugraph, ELP, Brussels) calculates the momentary vector of force extending downward from the center of gravity of the body and its movement around the vertical axis over time. Two related parameters are measured during both the eyes open and eyes closed recording epochs, i.e. the length of the vector's path (POS-L1 for eyes open and POS-L2 for eyes closed, in mm), and the area or surface circumscribed by the vector (POS-S1 for eyes open and POS-S2 for eyes closed, in mm²).

Subjective evaluations of mood, sedation and driving quality were assessed using a series of visual analogue scales (100 mm). The subjects were

instructed to rate their subjective feelings using a 16-item mood scale which provides three factor analytically defined summary scores for 'alertness', 'contentedness', and 'calmness' (Bond and Lader, 1974). The driving instructor rated each subject's driving quality and apparent sedation at the conclusion of each driving test, using two 100 mm visual analogue scales.

Subjective evaluations of sleep quality and duration were assessed using the Groningen Sleep Quality Questionnaire (Mulder-Hajonides van der Meulen, 1981) and an estimate of total sleep time. Two questions concerning nocturnal awakenings in the Groningen Sleep Quality Questionnaire were omitted due to the forced awakening at 04:00 hrs. Total scores on the sleep quality questionnaire could range between 0 (no complaints) and 12 (maximum number of complaints).

Procedure

Subjects were individually trained to perform the driving and laboratory tests. One week before the first treatment period subjects slept in the same facilities as during treatment periods, to overcome possible sleep disturbances associated with sleeping in an unfamiliar environment. On the morning following this habituation night subjects rehearsed all tests including driving.

Treatment periods started in the evening of Day 1, when the subjects arrived at the site at approximately 20:00 hours, and lasted until Day 2, when they were transported home after the driving test, at approximately 10:15 hours. On arrival at the sleeping facility in each treatment period, subjects' eligibility was verified. They were questioned about adverse events and use of medication since their last visit, and about recent use of coffee, alcohol and food. Vital signs were recorded, breath was assayed for alcohol using a breath analyzer (Lion Alcolmeter SD-400, Vale of Glamorgan, UK), and urine was assayed for presence of drugs (Triage 8 Panel Drugs of Abuse, Biosite Diagnostics, San Diego, USA). Pregnancy tests were performed for all women. Subjects ingested the first part of their medication at 23:00 hours and retired to bed. After a wake-up call, the subjects ingested the second part of their medication at 04:00 hours and were instructed to resume sleeping. They were awakened again by

CHAPTER 1

telephone 3 hrs later at 7:00 hours, and instructed to get dressed and to prepare for vital signs recording. Between 07:30 hours and 08:15 hours subjects performed cognitive and psychomotor tests and rated their subjective feelings and sleep. Driving performance was assessed between 9:00 and 10:00 hours, i.e. 10-11 hrs after ingestion of the evening dose, and between 5-6 hrs after ingestion of the middle-of-the-night dose. Upon completion of the driving test instructors rated subjects' driving quality and their appearance of being sedated.

Statistical analyses

Sample size was based on a power calculation for detecting a minimum treatment difference of 2.0 cm on SDLP with at least 90% power, using a two-sided t-test at a significance level of 5%, and assuming a within subject standard deviation of 2.1 cm, as estimated in previous studies conducted by the Maastricht University research group (Vermeeren, 2004). A treatment difference of 2.4 cm in SDLP was considered to be clinically relevant, as it corresponds to the effects found for alcohol while mean blood alcohol concentration was 0.5 mg/ml in a group of social drinkers using the same driving test (Louwerens et al., 1987).

Pharmacodynamic parameters from the road tracking test and other psychomotor and cognitive tests were analyzed by a mixed model analysis of variance (ANOVA) with fixed factors of treatment, sequence and period, and a random effect of subject within sequence using the SAS statistical program (version 8.2; SAS Institute Inc., Cary, NC.). To determine presence of residual effects, four a priori drug-placebo contrasts were made using the least square means procedure.

Analyses of residual effects were performed on the full-analysis-set (FAS) and the all- subjects-completed-set (ASCS) as described in a predefined analysis plan. The FAS consisted of 28 subjects that had received at least one dose of double-blind medication and had at least one valid post-dosing assessment of the SDLP. As a total of three subjects (10.7%) were withdrawn from the FAS, the analysis was repeated using the 25 subjects who completed

the study without protocol deviations (ASCS). Results of residual effects presented in this paper are based on the ASCS analyses. FAS analyses are only reported in case of diverging results. Descriptive summary statistics presented of adverse events were calculated based on the FAS.

RESULTS

Table 1 shows mean \pm SE values for each performance parameter and subjective evaluations in each treatment condition. Table 2 presents the mean differences from placebo and 95% confidence intervals of each treatment condition for the performance parameters and subjective evaluations.

Highway Driving Test

Six driving tests performed by a total of four subjects (16% relative to 25 subjects comprising the ASCS) were terminated prematurely because the driving instructor judged the subject to be too drowsy to continue safely. It subsequently appeared that five of the tests were terminated following middle-of-the night administration of an active hypnotic drug (10% relative to 50 driving tests). Three subjects were stopped before scheduled completion of the test after middle-of-the-night administration of gaboxadol. After middle-of-the-night administration of zolpidem, one subject was stopped and another, whose test was also prematurely terminated after middle-of-the-night administration of gaboxadol, did not start the driving test after middle-of-the-night administration of zolpidem, due to drug-related adverse events (dizziness, nausea and vomiting). In addition, the latter subject did not complete the test following evening administration of gaboxadol. The Standard Deviation of Lateral Position (SDLP) scores were calculated from the data collected until termination of each ride. None of the subjects was stopped prematurely following placebo or zopiclone administration.

Overall analysis of SDLP showed that there were significant differences in treatment effects ($F_{4,91}=7.55$, $p<0.001$). Mean increases in SDLP as compared with placebo were +1.28 cm, +2.53 cm, +2.73 cm, and +3.46 cm for evening

CHAPTER 1

administration of gaboxadol and zopiclone, and middle-of-the-night administration of gaboxadol and zolpidem, respectively (figure 1).

Table 1. Mean (\pm SE) of performance and mood parameters in each treatment condition (n=25)

	placebo	gaboxadol evening	zopiclone evening	gaboxadol night	zolpidem night
<i>Driving Test</i>					
Prematurely	0	1	0	3	2
SDLP (cm)	17.79 (0.57)	19.07 (0.78)	20.32 (0.66)	20.52 (0.93)	21.09 (0.84)
SDSP (km/h)	1.66 (0.09)	1.92 (0.10)	1.91 (0.09)	1.90 (0.13)	1.91 (0.12)
<i>Critical Tracking Test</i>					
Critical Frequency	3.94 (0.14)	3.87 (0.12)	3.82 (0.14)	3.65 (0.19)	3.51 (0.14)
<i>Divided Attention</i>					
Average Tracking	15.87 (0.87)	17.30 (0.81)	18.37 (0.80)	19.71 (0.86)	20.03 (0.91)
Target Detection	1745 (64)	1850 (73)	1869 (76)	1929 (65)	1929 (58)
<i>Digit Symbol</i>					
Correct Encodings	80.4 (2.6)	80.2 (2.2)	77.2 (2.3)	76.6 (2.4)	73.9 (2.3)
<i>Word Learning Test</i>					
Immediate Recall	13.4 (0.4)	13.5 (0.3)	13.2 (0.4)	13.2 (0.4)	12.7 (0.4)
Delayed Recall	11.0 (0.7)	11.1 (0.6)	9.7 (0.7)	10.3 (0.7)	8.7 (0.6)
Recognition Score	28.6 (0.3)	28.2 (0.3)	27.0 (0.5)	27.8 (0.5)	27.4 (0.4)
Recognition	716 (20)	751 (21)	802 (27)	756 (26)	809 (25)
<i>Body Sway</i>					
Eyes open: Vector	351 (9.7)	356 (11.7)	384 (14.4)	377 (14.3)	391 (16.6)
Eyes open: Vector	104 (14.5)	111 (12.9)	144 (16.8)	145 (21.2)	182 (28.0)
Eyes closed: Vector	355 (10.7)	355 (12.3)	356 (12.8)	390 (15.5)	386 (16.3)
Eyes closed: Vector	84 (7.5)	82 (7.9)	103 (10.9)	148 (18.3)	164 (36.2)
<i>Subjective</i>					
Alertness	69.9 (3.5)	67.0 (3.5)	66.7 (3.1)	46.6 (4.4)	53.5 (3.9)
Contentedness	75.2 (3.2)	75.2 (2.7)	76.4 (2.6)	67.9 (3.4)	69.4 (2.8)
Calmness	77.3 (3.3)	81.2 (2.6)	80.8 (2.4)	76.2 (3.3)	74.8 (2.4)
Driving Quality	80.5 (1.5)	73.4 (2.0)	72.4 (2.3)	68.2 (3.4)	71.9 (2.4)
Sedation	11.1 (2.5)	21.4 (3.9)	23.1 (4.5)	34.9 (5.7)	29.1 (5.6)

Table 2. Mean difference and 95% confidence interval from placebo for each treatment condition (n=25)

	gaboxadol evening		zopiclone evening		gaboxadol night		zolpidem night	
	Δ	95%CI	Δ	95%CI	Δ	95%CI	Δ	95%CI
<i>Driving Test</i>								
SDLP (cm)	+1.28	-0.10–2.67	+2.53	1.14–3.91***	+2.73	1.34–4.11***	+3.46	2.06–4.86***
SDSP (km/h)	+0.25	0.10–0.41**	+0.25	0.10–0.41**	+0.24	0.08–0.39**	+0.26	0.10–0.41**
<i>Critical Tracking Test</i>								
Critical Frequency (rad/s)	-0.07	-0.27–0.12	-0.12	-0.31–0.08	-0.29	-0.48– -0.09**	-0.42	-0.31– -0.08***
<i>Divided Attention Test</i>								
Average Tracking Error (mm)	+1.43	0.12–2.75*	+2.51	1.19–3.82***	+3.85	2.53–5.17***	+4.16	2.84–5.48***
Target Detection Reaction Time (ms)	+105	-10–219	+123	9–238*	+184	69–299**	+184	69–298**
<i>Digit Symbol Substitution Test</i>								
Correct Encodings (#)	-0.2	-2.8– -2.4	-3.2	-5.8– -0.6*	-3.8	-6.4– -1.2**	-6.5	-9.1– -3.9***
<i>Word Learning Test</i>								
Immediate Recall Score (#)	+0.1	-0.5–0.8	-0.1	-0.8–0.5	-0.2	-0.8–0.5	-0.7	-1.3–0.0*
Delayed Recall Score (#)	+0.1	-1.0–1.2	-1.3	-2.4– -0.3*	-0.7	-1.8–0.4	-2.28	-3.4– -1.2***
Recognition Score (#)	-0.4	-1.3–0.5	-1.6	-2.5– -0.7***	-0.7	-1.6–0.2	-1.2	-2.1– -0.3*
Recognition Reaction Time (ms)	+35	-9–78	+86	42–129***	+40	-4–83	+93	49–136***
<i>Body Sway</i>								
Eyes open: Vector Length (mm)	+5	-19–29	+34	9–58*	+27	3–51*	+40	16–65**
Eyes open: Vector Surface (mm ²)	+7	-25–39	+40	8–71*	+41	9–73*	+78	46–110***
Eyes closed: Vector Length (mm)	0	-27–28	+1	-27–28	+35	8–63*	+32	4–59*
Eyes closed: Vector Surface (mm ²)	-3	-46–39	+19	-24–61	+63	21–106**	+79	37–122***

Table 2. continued from p. 33

	gaboxadol evening		zopiclone evening		gaboxadol night		zolpidem night	
	Δ	95%CI	Δ	95%CI	Δ	95%CI	Δ	95%CI
<i>Subjective Evaluation</i>								
Alertness	-2.9	-11.1–5.3	-3.2	-11.3–5.0	-23.2	-31.4– -15.1 ^{***}	-16.4	-24.5– -8.2 ^{**}
Contentedness	0.0	-5.0–5.0	+1.2	-3.8–6.2	-7.3	-12.3– -2.3 ^{**}	-5.8	-10.8– -0.8 [*]
Calmness	+3.9	-0.2–8.0	+3.5	-0.6–7.6	-1.1	-5.2–3.0	-2.6	-6.6–1.5
Driving Quality	-7.1	-12.7– -1.5 [*]	-8.2	-13.8– -2.5 ^{**}	-12.4	-18.0– -6.8 ^{***}	-9.5	-15.2– -3.8 ^{**}
Sedation	+10.3	-0.3– 20.8	+12.0	1.5–22.6 [*]	+23.8	13.2–34.4 ^{***}	+18.6	7.9–29.4 ^{***}

Significant differences from placebo: * p < 0.05; ** p < 0.01; *** p < 0.001

HYPNOTICS, DRIVING AND HEALTHY YOUNG VOLUNTEERS

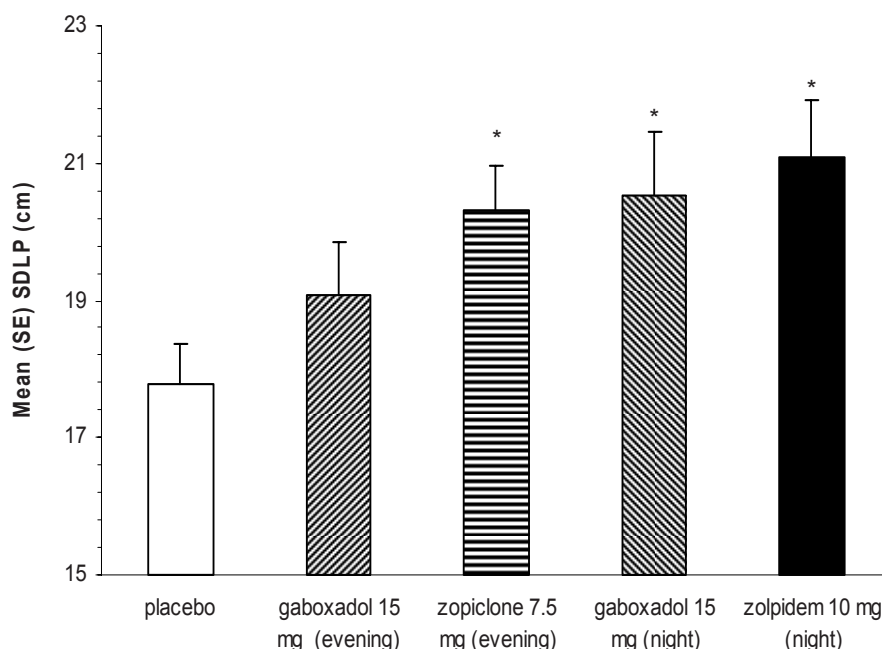


Figure 1. Mean (+SE) of the Standard Deviation of Lateral Position (SDLP) in each treatment condition. Indicated are significant drug-placebo differences ($p<0.001$)

Drug-placebo comparisons showed that these increases were significant for all treatments ($p\leq 0.001$), except the smallest, i.e. evening administration of gaboxadol ($p<0.070$). The latter effect was significant, however, according to analyses of the FAS (+1.40 cm; $p=0.0422$). For the remaining treatments results based on the FAS were similar to those based on the ASCS.

The ability to keep a constant speed, as measured by Standard Deviation of Speed (SDSP), differed significantly between treatments ($F_{4,91}=4.11$, $p=0.0042$). The variability in speed was significantly increased following all hypnotics as compared with placebo (all $p<0.004$).

Critical Tracking Test

A significant overall treatment effect was found in tracking performance, as measured by the average critical frequency ($F_{4,92}=6.37$, $p<0.0001$). Drug-placebo comparisons revealed this was due to significant impairment after

middle-of-the-night administration of gaboxadol and zolpidem ($p=0.0040$ and $p<0.0001$, respectively).

Divided Attention Test

There were significant differences between treatments in both subtasks of the divided attention task (tracking: $F_{4,92}=13.52$, $p<0.0001$ and target detection: $F_{4,92}=3.42$, $p=0.0119$). Drug-placebo comparisons revealed that tracking error and target detection reaction times were significantly increased after middle-of-the-night administration of zolpidem and gaboxadol ($p<0.0001$ for both treatments in tracking error and $p<0.002$ for both treatments in target detection), and evening administration of zopiclone ($p=0.0003$ and $p=0.0351$, respectively). Following evening administration of gaboxadol, tracking performance was significantly impaired ($p=0.0333$), but not speed of target detection ($p<0.075$). The latter was significantly impaired, however, according to analyses of the FAS ($p=0.0346$).

Digit Symbol Substitution Test

Total number of correct encodings in the DSST differed significantly between treatments ($F_{4,92}=8.62$, $p<0.0001$). Compared with placebo, number of correct encodings was significantly decreased after middle-of-the-night administration of zolpidem and gaboxadol ($p<0.0001$ and $p=0.0047$, respectively), and evening administration of zopiclone ($p=0.0153$). After evening administration of gaboxadol no significant effect was found.

Word Learning Test

Whereas there were no significant differences between treatments in immediate recall scores ($F_{4,92}=1.83$, $p>0.1$), analyses revealed highly significant treatment effects in delayed recall scores ($F_{4,92}=6.65$, $p<0.0001$), recognition scores ($F_{4,92}=3.89$, $p<0.0058$) and recognition reaction times ($F_{4,92}=6.21$, $p=0.0002$). Both active controls, but not gaboxadol, had significant impairing effects on memory performance. Compared with placebo, evening administration of zopiclone and middle-of-the-night administration of zolpidem resulted in lower

delayed recall scores ($p=0.0163$ and $p<0.0001$, respectively), fewer words recognized correctly ($p=0.0007$ and $p<0.0123$, respectively), and slower responses (both $p<0.0002$).

Body Sway

Analysis of postural stability revealed significant overall treatment effects on length and surface of the body sway vector with eyes open (POS-L1, $F_{4,92}=4.25$, $p<0.0033$; and POS-S1, $F_{4,92}=7.66$, $p<0.0001$, respectively) and eyes closed (POS-L2: $F_{4,92}=3.40$, $p=0.0122$; and POS-S2: $F_{4,92}=6.16$, $p=0.0002$, respectively).

Drug-placebo analyses showed that all active treatments, except evening administration of gaboxadol, significantly impaired postural stability. Gaboxadol significantly affected all parameters when administered in the middle-of-the-night (POS-L1: $p=0.0289$, POS-S1: $p=0.0116$; POS-L2: $p=0.0130$; POS-S2: $p=0.0039$), whereas no effects were found after administration in the evening at bedtime. Middle-of-the-night administration of zolpidem significantly affected all parameters (POS-L1: $p=0.0013$, POS-S1: $p<0.0001$, POS-L2: $p=0.0252$; and POS-S2: $p=0.0004$). Evening administration of zopiclone had significant effects on body sway with eyes open (POS-L1: $p=0.0071$ and POS-S1: $p=0.0153$), but not on sway with eyes closed.

Subjective Evaluations

The driving instructors' ratings of subjects' driving quality and their appearance of being sedated differed significantly between treatments ($F_{4,91}=5.27$, $p=0.0007$; $F_{4,91}=5.73$, $p=0.0004$). They rated driving quality to be significantly worse than placebo following all hypnotics, i.e. evening administration of gaboxadol and zopiclone ($p=0.0135$, and $p=0.0048$, respectively) and middle-of-the-night administration of gaboxadol and zolpidem ($p<0.0001$: and $p<0.0013$, respectively). In addition, instructors rated subjects to appear clearly more sedated after middle-of-the-night administration of gaboxadol and zolpidem, and after evening administration of zopiclone as compared with placebo ($p<0.0001$, $p=0.0008$, $p=0.0260$, respectively). The difference between evening

administration of gaboxadol and placebo just failed to reach significance according to ASCS analysis ($p < 0.057$), but was significant according to FAS analysis ($p = 0.0271$).

The subjects' ratings of their feelings of alertness and contentedness were significantly different between treatments ($F_{4,92} = 12.09$, $p < 0.0001$; $F_{4,92} = 4.70$, $p = 0.0017$, respectively). They rated themselves as less alert and contented than placebo after the middle-of-the-night administrations of gaboxadol ($p < 0.0001$ and $p = 0.0046$, respectively) and zolpidem ($p = 0.0001$, and $p = 0.0237$, respectively). Evening administration of gaboxadol and zopiclone had no significant effects on subjective feelings. A significant overall treatment effect on calmness was found ($F_{4,92} = 3.8$, $p = 0.0067$), but ratings did not differ significantly between drugs and placebo.

Subjective sleep quality and estimated total sleep times differed significantly between treatments ($F_{4,92} = 4.41$ and 3.67 , $p = 0.0026$ and 0.0080 , respectively). The mean \pm SE number of complaints decreased significantly from 4.3 ± 0.8 after placebo to 2.4 ± 0.4 and 2.0 ± 0.3 after evening administrations of gaboxadol ($p = 0.011$) and zopiclone ($p = 0.002$), respectively. No significant differences were found between placebo and the two middle-of-the-night treatments. Mean \pm SE estimated total sleep time increased from 402 ± 14 minutes after placebo to 445 ± 8 and 454 ± 5 minutes after evening doses of gaboxadol ($p = 0.0008$) and zopiclone ($p < 0.0001$), and to 422 ± 12 and 435 ± 8 minutes after middle-of-the-night administrations of gaboxadol ($p = 0.113$) and zolpidem ($p = 0.0086$), respectively.

Safety

An overview of the incidence of reported adverse events is shown in Table 3. There were no serious adverse events. Overall the most frequently reported adverse events in this study were dizziness, headache, somnolence and nausea. The highest number of complaints occurred after the middle-of-the-night administrations of both gaboxadol and zolpidem. After evening administration of gaboxadol the highest incidence of reported adverse events were headaches and somnolence, and after evening administration of zopiclone

they only reported headaches. All adverse events were mild or moderate and resolved without treatment.

Tabel 3. Incidence of reported adverse events

	All treatments (n=28)	placebo (n=28)	gaboxadol evening (n=27)	zopiclone evening (n=28)	gaboxadol night (n=26)	zolpidem night (n=26)
Dizziness	10 (36%)	0	0	1 (4%)	9 (35%)	4 (14%)
Headache	7 (25%)	1 (4%)	4 (15%)	3 (12%)	1 (4%)	1 (4%)
Somnolence	6 (21%)	0	3 (11%)	0	3 (12%)	1 (4%)
Nausea	5 (18%)	0	0	0	5 (19%)	3 (11%)
Abnormal	2 (7%)	0	0	0	2 (8%)	0
Dysguesia	2 (7%)	1 (4%)	0	0	0	1 (4%)
Fatigue	2 (7%)	0	1 (4%)	0	1 (4%)	0
Mental	2 (7%)	0	1 (4%)	0	1 (4%)	0
Vomiting	2 (7%)	0	1 (4%)	0	1 (4%)	2 (7%)

DISCUSSION

The results of this study show that gaboxadol 15 mg administered at bedtime can have residual effects until at least 11 hours after intake, as shown by significant or nearly significant effects on performance in the driving test and the divided attention test. Use of gaboxadol 15 mg in the middle-of-the-night was clearly associated with residual effects on driving, as reflected by a significant increase in SDLP, and psychomotor performance, but not on memory. The middle-of-the-night dose of gaboxadol significantly impaired performance in all tests between 3.5 and 6 hrs after intake, except the word learning test.

Results of the driving test are most relevant with respect to traffic safety. Gaboxadol 15 mg produced a nearly significant +1.3 cm mean increase in SDLP above the placebo level, between 10 and 11 hrs after evening administration ($p < 0.070$), which was significant ($p < 0.042$) based on analyses of the full-analysis set. The severity of the effect, however, is on average of lesser magnitude than that produced by alcohol in a previous study while subjects drove with blood alcohol concentrations (BAC) of 0.5 mg/mL (+2.4 cm)

CHAPTER 1

(Louwerens et al., 1987), which is the legal limit for driving a car in most countries. Still, analyses with the same set showed that the driving instructors were able to judge the subjects to be significantly more sedated after this dose compared with placebo. Furthermore, one subject was stopped by the driving instructor due to excessive drowsiness following the evening dose of gaboxadol, and subjects drove with significantly more variability in speed following gaboxadol as compared with placebo (+0.25 km/h).

In addition to the effects on driving performance, the evening dose of gaboxadol was also found to have minor but significant effects on performance in the divided attention test. These effects were unexpected as three previous studies did not find significant residual effects of gaboxadol in doses up to 20 mg administered at bedtime (Lundahl et al., 2006, Mathias et al., 2005, Walsh et al., 2007). The discrepancy may partly explained by the tests used. Similar to previous findings, evening doses of gaboxadol in the present study had no significant residual effects on performance in relatively short psychomotor tests (critical tracking, digit symbol substitution and body sway) and the memory test. The standardized highway driving test and the divided attention test have been found to be among the most sensitive tests to assess drug-induced sedation (e.g. Vermeeren et al., 2002), probably because they are tests of longer duration and continuous high attentional demands. Post hoc inspection of mean SDLP scores per 15 minute intervals of the test showed that performance after an evening dose of gaboxadol was similar to placebo during the first 15 minute interval, but started to decline thereafter. This suggests that these effects may be counteracted by a temporary increase in effort. As effort can only be increased for a limited period of time, performance decreases thereafter (Sanders, 1983). For this reason shorter tests, as used in previous studies, may have failed to show residual effects of bedtime doses of gaboxadol. Following evening administration of zopiclone and middle-of-the-night doses of gaboxadol and zolpidem impairment was already present during the first interval and did not increase further with time on task, suggesting that increased effort could not compensate the residual effects of these treatments.

Middle-of-the-night administration of gaboxadol 15 mg produced a significant +2.7 cm mean increase in SDLP above the placebo level, between 5 and 6 hrs after administration. This effect is of greater magnitude than that produced by alcohol while subjects drove with BACs of 0.5 mg/mL (Louwerens et al., 1987). In addition, the driving instructor terminated three tests prematurely due to excessive drowsiness of the subjects.

The middle-of-the-night dose of zolpidem 10 mg significantly impaired performance in all tests the following morning. One subject did not start the driving test due to dizziness and nausea, and another was stopped prematurely by the driving instructor due to excessive drowsiness following this dose. The mean increase in SDLP between 5 and 6 hrs after administration was +3.5 cm. This closely corresponds to the increase in SDLP of +3.8 cm found between 4 and 5 hrs after middle-of-the-night administration of the same dose in a study with 30 healthy volunteers by (Verster et al., 2002). These investigators did not find significant effects of zolpidem 10 mg on word learning, critical tracking, divided attention and DSST performance, however, which is probably due to the later time of testing. Laboratory testing in their study started at 6 hrs after administration, whereas it started at 4.5 hours after administration in the present study. The results of the present study confirm the importance of instructing patients to ingest zolpidem 10 mg only prior to a full eight hours of uninterrupted sleep and not in the middle-of-the-night (cf. Verster et al., 2007).

The evening dose of zopiclone 7.5 mg had significant residual effects on driving, body sway, word learning, DSST, and divided attention, but not on tracking performance. The average increase in SDLP (+2.53) found in the present study confirms our previous conclusions that zopiclone 7.5 mg can produce residual effects on driving comparable to those found for alcohol when BAC 0.5 mg/mL or more, and that patients should be warned accordingly (Vermeeren et al., 1998, Vermeeren et al., 2002). The latter is particularly important because results from the subjective rating scales showed that subjects themselves were not aware of any residual effects of the evening dose of zopiclone. Although they felt less alert and contented on mornings following

middle-of-the-night administration of gaboxadol and zolpidem, they failed to notice their reduced alertness following zopiclone.

A limitation of the present study may be that the subjects were medication naïve healthy volunteers. The results may overestimate the impairing effects on driving performance as compared to those in insomniacs using hypnotics. First, it is sometimes argued that hypnotics may improve daytime cognitive performance in insomniacs, as a result of improving sleep. Although subjects in the present study were healthy young volunteers without complaints of insomnia, they did rate the quality of their sleep to be better and their sleep duration to be longer after evening administration of gaboxadol and zopiclone as compared to placebo. However, no improvement in performance was detected after use of these drugs, in any of the tasks. On the contrary, following zopiclone most performance scores showed impairment. This indicates that potentially positive effects of sleep improvement could not compensate the residual sedative effects of the drugs on performance in our subjects, at least not completely.

Second, a majority of insomniacs use hypnotics for prolonged periods (Curran et al., 2003), which consequently may result in the development of tolerance to the impairing effects of hypnotics. Experimental studies investigating the effects of hypnotics on actual driving performance in chronic users do not exist, however. Epidemiological studies have shown that there is still a significantly increased risk of crash involvement after one month of treatment, suggesting that tolerance was not complete (Neutel, 1998). It remains therefore to be determined whether the results of hypnotics' effects on sleep, their residual sedation and tolerance is the same in insomniac patients frequently using hypnotics as in healthy volunteers.

A remarkable finding was the lack of effects of gaboxadol on memory. In contrast to the effects of zolpidem and zopiclone, no significant effects were found on any of the four performance parameters in the word learning test after gaboxadol, irrespective of the time of administration. This cannot be explained by the pharmacokinetic factors since the middle-of-the-night dose of gaboxadol significantly impaired performance on all other tests, indicating that it was

clearly CNS active at the time of testing. An explanation is therefore most likely related to its receptor binding profile. Gaboxadol is primarily an agonist at extrasynaptic α_4 - and α_6 -containing GABA_A receptors, whereas the amnesic effects of benzodiazepines and zolpidem seem to be mediated by their affinity for α_1 and α_5 subunits (Savic et al., 2005). According to a recent review by Savic et al. (2005) the α_5 subunits, mainly expressed in the hippocampus, modulate the effects of benzodiazepines on explicit memory, while α_1 subunits are substantially involved in procedural memory as well. Since gaboxadol has a relatively low affinity for these receptor subunits, it may produce less memory disturbances than other GABAergic hypnotics.

In conclusion, the results of this study indicate that gaboxadol 15 mg can produce minor residual effects on driving between 10 and 11 hrs after evening administration. Administration later at night is associated with moderately impairing residual effects on driving and psychomotor performance until 6 hrs after intake, but not on memory. Results also show that zolpidem 10 mg taken in the night has moderately severe impairing effects on driving the next morning at least until 6 hours after intake. This confirms the importance of instructing patients to ingest zolpidem 10 mg only prior to a full eight hours of uninterrupted sleep. Finally this study shows that zopiclone 7.5 mg taken at bedtime consistently impairs driving the next morning at least until 11 hours after intake, while subjects seem unaware of this effect. This stresses the importance of warning patients concerning residual effects hypnotics by their physicians or pharmacists.

REFERENCES

- Barbone, F., McMahon, A. D., Davey, P. G., Morris, A. D., Reid, I. C., McDevitt, D. G. & Macdonald, T. M. Association of road-traffic accidents with benzodiazepine use. *Lancet*, 1998, 352: 1331-1336.
- Bond, A., & Lader, M. The use of analogue scales in rating subjective feelings. *Br J Med Psychol*, 1974, 47: 211-218.

CHAPTER 1

- Curran, H. V., Collins, R., Fletcher, S., Kee, S. C. Y., Woods, B. & Iliffe, S. Older adults and withdrawal from benzodiazepine hypnotics in general practice: Effects on cognitive function, sleep, mood and quality of life. *Psychol Med*, 2003, 33: 1223-1237.
- Deacon, S., Staner, L., Staner, C., Legters, A., Loft, H. & Lundahl, J. Effect of short-term treatment with gaboxadol on sleep maintenance and initiation in patients with primary insomnia. *Sleep*, 2007, 30: 281-287.
- Deacon, S., Staner, L., Staner, C., Vorstrup, S., & Lundahl, J. Acute administration of gaboxadol improves sleep initiation and maintenance in patients with primary insomnia. *Sleep*, 2005, 28: A240-A240.
- Ebert, B., Wafford, K. A. & Deacon, S. Treating insomnia: Current and investigational pharmacological approaches. *Pharmacol Therapeut*, 2006, 112: 612-629.
- Faulhaber, J., Steiger, A. & Lancel, M. The GABAA agonist THIP produces slow wave sleep and reduces spindling activity in NREM sleep in humans. *Psychopharmacology*, 1997, 130: 285-291.
- Jex, H. R., McDonnell, J. D. & Phatak, A. V. A "critical" tracking task for man-machine research related to the operator's effective delay time. I. Theory and experiments with a first-order divergent controlled element. NASA CR-616. *NASA Contract Rep NASA CR*, 1966: 1-105.
- Kapteyn, T. S., Bles, W., Nijokiktijen, C. J., Kodde, L., Massen, C.H., & Mol, J. M. Standardization in platform stabilometry being part of posturography. *Agressologie*, 1983, 24: 321-326.
- Lancel, M., Wetter, T. C., Steiger, A. & Mathias, S. Effect of the GABAA agonist gaboxadol on nocturnal sleep and hormone secretion in healthy elderly subjects. *Am J Physiol. Endoc M*, 2001, 281: E130-137.
- Louwerens, J. W., Gloerich, A. B. M., Vries, D., G., Brookhuis, K. A. & O'Hanlon, J. F. The relationship between drivers' blood alcohol concentration (BAC) and actual driving performance during high speed travel. *Alcohol Drug Traffic Safe*, 1987, T86: 183-186.
- Lund, J., Helboe, T. & Mengel, H. Absorption, metabolism, and excretion profile of gaboxadol in humans. *Sleep*, 2006, 29: A41.

- Lund, J., Lundahl, J., Nielsen, G. M. & Mengel, H. The pharmacokinetic properties of gaboxadol, a new hypnotic, in young and elderly men. *Sleep*, 2005, 28: A48.
- Lundahl, J., Staner, L., Staner, C. & Deacon, S. The selective extrasynaptic GABA_A agonist, gaboxadol, improves sleep maintenance and enhances slow wave sleep in adult patients with primary insomnia. *J Sleep Res*, 2006, 15: 194-195.
- Mathias, S., Steiger, A., Lancel, M. The GABA_A agonist gaboxadol improves the quality of post-nap sleep. *Psychopharmacology*, 2001, 157: 299-304.
- Mathias, S., Zihl, J., Steiger, A. & Lancel, M. Effect of repeated gaboxadol administration on night sleep and next-day performance in healthy elderly subjects. *Neuropsychopharmacol*, 2005, 30: 833-841.
- Moskowitz, H. Laboratory studies of the effects of alcohol on some variables related to driving. *J Saf Res*, 1973, 5: 185-199.
- Mulder-Hajonides Van Der Meulen, W. R. E. H. *Measurement of subjective sleep quality*, Amsterdam, Elsevier, 1981.
- Neutel, I. Benzodiazepine-related traffic accidents in young and elderly drivers. *Human Psychopharm Clin*, 1998, 13: S115-S123.
- O'Hanlon, J. F. Driving performance under the influence of drugs: rationale for, and application of, a new test. *Br J Clin Pharmacol*, 1984, 18 Suppl 1: 121s-129s.
- Ramaekers, J. G., Muntjewerff, N. D., Uiterwijk, M. M. C., Van Veggel, L. M. A., Patat, A., Durrieu, G., & O'Hanlon, J. F. A study of the pharmacodynamic interaction between befloradone and ethanol on performance and mood in healthy volunteers. *J Psychopharmacol*, 1996, 10: 288-294.
- Rey, A. *L'examen clinique en psychologie.*, Paris, Presses Universitaires de France, 1964.
- Sanders, A. F. Towards a model of stress and human performance. *Acta Psychol*, 1983, 53: 61-97.

CHAPTER 1

- Savic, M. M., Obradovic, D. I., Ugresic, N. D. & Bokonjic, D. R. Memory effects of benzodiazepines: memory stages and types versus binding-site subtypes. *Neural Plast*, 2005, 12: 289-298.
- Schultz, B., Aaes Jorgensen, T., Bogeso, K. P. & Jorgensen, A. Preliminary studies on the absorption, distribution, metabolism, and excretion of THIP in animal and man using ¹⁴C-labelled compound. *Acta Pharmacol Tox*, 1981, 49: 116-124.
- Storustovu, S. I. & Ebert, B. Pharmacological characterization of agonists at delta-containing GABAA receptors: Functional selectivity for extrasynaptic receptors is dependent on the absence of gamma2. *J Pharmacol Exp Ther*, 2006, 316: 1351-1359.
- Swainston Harrison, T. & Keating, G. M. Zolpidem: a review of its use in the management of insomnia. *CNS Drugs*, 2005, 19: 65-89.
- Vermeeren, A. Residual effects of hypnotics: epidemiology and clinical implications. *CNS Drugs*, 2004, 18: 297-328.
- Vermeeren, A., Danjou, P. E. & O'Hanlon, J. F. Residual effects of evening and middle-of-the-night administration of zaleplon 10 and 20 mg on memory and actual driving performance. *Hum Psychopharm*, 1998, 13: S98-S107.
- Vermeeren, A., O'Hanlon, J. F., Declerck, A. C., & Kho, L. Acute effects of zolpidem and flunitrazepam on sleep, memory and driving performance, compared to those of partial sleep deprivation and placebo. *Acta Therap*, 1995, 21: 47-64.
- Vermeeren, A., Riedel, W. J., Van Boxtel, M. P., Darwish, M., Paty, I. & Patat, A. Differential residual effects of zaleplon and zopiclone on actual driving: a comparison with a low dose of alcohol. *Sleep*, 2002, 25: 224-231.
- Verster, J. C., Veldhuijzen, D. S. & Volkerts, E. R. Residual effects of sleep medication on driving ability. *Sleep Med Rev*, 2004, 8: 309-325.
- Verster, J. C., Volkerts, E. R., Olivier, B., Johnson, W. & Liddicoat, L. Zolpidem and traffic safety - the importance of treatment compliance. *Curr Drug Safe*, 2007, 2: 220-226.

- Verster, J. C., Volkerts, E. R., Schreuder, A. H., Eijken, E. J., Van Heuckelum, J. H., Veldhuijzen, D. S., Verbaten, M. N., Paty, I., Darwish, M., Danjou, P. & Patat, A. Residual effects of middle-of-the-night administration of zaleplon and zolpidem on driving ability, memory functions, and psychomotor performance. *J Clin Psychopharmacol*, 2002, 22: 576-583.
- Walsh, J. K., Deacon, S., Dijk, D. J. & Lundahl, J. The selective extrasynaptic GABAA agonist, gaboxadol, improves traditional hypnotic efficacy measures and enhances slow wave activity in a model of transient insomnia. *Sleep*, 2007, 30: 593-602.

CHAPTER 1

CHAPTER 2

Highway driving in elderly the morning after bedtime use of hypnotics: a comparison between temazepam 20 mg, zopiclone 7.5 mg and placebo

Accepted for publication as:

Leufkens TRM, Vermeeren A. Highway driving in elderly the morning after bedtime use of hypnotics: a comparison between temazepam 20 mg, zopiclone 7.5 mg and placebo. *Journal of Clinical Psychopharmacology*.

ABSTRACT

A major problem related to hypnotic drug use is residual sedation the morning after bedtime administration. This constitutes a particular safety hazard for patients who have to drive a car the next morning. Information on the severity of residual effects is mainly derived from studies conducted with young healthy volunteers. However, the majority of users of hypnotics are older people, who may be more sensitive to drug effects.

The aim of this study was to evaluate the residual effects the morning after evening doses of temazepam 20 mg and zopiclone 7.5 mg on driving performance in healthy elderly drivers.

Eighteen healthy elderly drivers (10 female and 8 male; mean age 64.3 years) participated in a double-blind, three-way crossover study. Treatments were single oral doses of temazepam 20 mg, zopiclone 7.5 mg and placebo administered at bedtime. Subjects performed a standardized highway driving test between 10 and 11 hours after hypnotic intake. Before and after the driving test cognitive performance was assessed.

Driving performance did not differ between temazepam and placebo, but was significantly impaired following zopiclone 7.5 mg ($p < 0.002$). The results of the laboratory tests were in line with the effects on driving of both hypnotics.

Temazepam 20 mg is unlikely to impair driving 10 hours or more after bedtime administration in healthy elderly aged 75 years or younger. Zopiclone 7.5 mg moderately impairs driving in elderly at least until 11 hours after administration. The magnitude of impairing effects in elderly was comparable to those found previously in younger volunteers.

INTRODUCTION

A major problem of hypnotic drug use is residual sedation the morning after bedtime administration. It results in an impairment of a number of behavioral and mental functions, such as psychomotor performance, visual perception, attention, memory and information processing (Vermeeren, 2004). This

constitutes a particular safety hazard for patients whose activity the next morning involves skilled work and in whom impairment of performance in daily activities, such as driving a car, could be a danger to themselves or others. Experimental studies on driving performance have shown that the duration and severity of the residual effects differ between hypnotics, depending on the hypnotic's half-life, the dose and formulation (Vermeeren, 2004). Being aware of the differences between hypnotics should enable physicians to select the safest alternative possible for patients who have to drive a car the next morning.

The benzodiazepine temazepam and the non-benzodiazepine zopiclone are among the most frequently prescribed hypnotic drugs (Busto et al., 2001, Kassam et al., 2006, Rosenberg, 2006). Temazepam in its commonly prescribed dose of 20 mg is considered to be safe for patients who need to drive a car the morning following evening administration (O'Hanlon and Volkerts, 1986, Vermeeren, 2004). Zopiclone, on the other hand, in its recommended dose of 7.5 mg, has been shown to produce moderately impairing residual effects on driving performance (Vermeeren et al., 1998, Vermeeren et al., 2002, Leufkens et al., in press). Information on these effects have, however, been mainly derived from experimental studies conducted in healthy young volunteers, whereas the majority of hypnotics users are elderly (Drake et al., 2003, Glass et al., 2005). Drug effects may be more pronounced in elderly drivers, due to age-related reductions in liver capacity and lean body mass. Additionally, with age, sensitivity to the hypnotic effects may be increased (Woodward, 1999). It is therefore possible that hypnotic drugs like temazepam 20 mg, that have no detectable residual effects in young, do have significant residual effects in older drivers. Yet, to date, the residual effects of hypnotics have never been investigated using tests of actual driving in elderly drivers.

There are studies that used laboratory tests to assess the residual effects of hypnotics in elderly, but these may be limited with respect to assessing drug effects on driving. For example, residual effects of temazepam 20 mg and zopiclone 7.5 mg on cognitive and psychomotor functions of healthy elderly were assessed using laboratory tests, such as choice reaction time and critical flicker fusion (Hemmeter et al., 2000). Results showed no significant residual

impairments. The lack of residual effects after zopiclone 7.5 mg suggests, however, that tests or procedures used in the study did not have sufficient sensitivity to detect effects on driving, because studies using tests of actual driving have consistently shown that zopiclone 7.5 mg has moderately impairing residual effects on driving in healthy young volunteers (Vermeeren et al., 1998, Vermeeren et al., 2002, Leufkens et al., in press).

The aim of the present study was to compare the residual effects of temazepam 20 mg, zopiclone 7.5 mg and placebo on actual driving performance in a group of 18 healthy elderly drivers using a standardized highway driving test. This test evolved from studies on driver fatigue and was standardized for assessing drug effects on actual driving performance in the early 1980s (O'Hanlon et al., 1982, O'Hanlon, 1984). It has subsequently been applied in over 75 drug studies (Ramaekers, 2003, Vermeeren, 2004, Theunissen et al., 2009, Vermeeren et al., 2009). The primary performance parameter is Standard Deviation of Lateral Position (SDLP, in cm) that can be interpreted as an index of weaving or course-keeping error. SDLP is a reliable characteristic of individual driving performance (test retest $r=0.7$ to 0.9) and has proven sensitive to many sedating drugs, including zopiclone 7.5 mg (Volkerts and O'Hanlon, 1988, Vermeeren et al., 1998, Vermeeren et al., 2002, Leufkens et al., in press).

METHODS

Subjects

Eighteen healthy elderly male and female drivers (ages 55-75) were recruited by means of advertisements in local newspapers. Subjects needed to possess a valid driving license and an average driving experience of at least 5000 km/year over the last three years. Volunteers were screened by a medical history questionnaire and a physical examination. The latter included a 12-lead ECG, blood chemistry and hematology, urinalysis and tests for drug of abuse (amphetamines, benzodiazepines, cannabis, cocaine, MDMA and opiates). Inclusion criteria were good health, body mass index (BMI) between 19 and 29

kg/m², and normal vision (corrected or uncorrected). Volunteers who met any of the following exclusion criteria could not participate in the study: any history or current evidence of any clinically significant physical or mental disorders, alcoholism or drug abuse; acute illness; use of medication known to affect driving performance; blood donation or participation in any other clinical trial within the previous three months; consumption of more than 6 beverages containing caffeine per day or more than 10 cigarettes per day, and drinking more than 21 alcohol containing beverages per week.

During participation use of caffeine was prohibited from 4 hours prior to arrival on treatment days, until discharge the next morning. Alcohol intake was not allowed from 24 hours prior to each dosing until discharge. Smoking was prohibited from arrival until discharge and eating was not permitted from arrival until breakfast.

All 18 subjects (10 females and 8 males) completed the study between November 2006 and February 2007. Their mean \pm SE age of was 64.3 ± 1.0 years and their mean \pm SE BMI was 24.0 ± 0.5 kg/m².

The study was conducted in accordance with the code of ethics on human experimentation established by the World Medical Association's Declaration of Helsinki (1964) and amended in Edinburgh (2000). The protocol was approved by the medical ethics committee of Maastricht University and University Hospital of Maastricht. Subjects were explained the aims, methods, and potential hazards of the study and they signed a written informed consent prior to any study-related assessments.

Design

The study was conducted according to a double-blind, three-way crossover design. Treatments were temazepam 20 mg, zopiclone 7.5 mg and placebo administered in identical looking capsules and ingested immediately before retiring to bed at 23:00 hours. Order of treatment was balanced by randomly assigning 6 treatment sequences residing in two Latin squares to 18 subjects.

Assessments

Residual effects were assessed using a battery of laboratory tests, a highway driving test and subjective rating scales, all of which have been previously found sensitive to the residual effects of hypnotics (Vermeeren et al., 1995, Vermeeren et al., 1998, Vermeeren et al., 2002, Verster et al., 2002, Leufkens et al., in press) and low doses of alcohol (Ramaekers, 1996, Vermeeren et al., 2002).

In the Standardized Highway Driving Test (O'Hanlon, 1984) the subject operates a specially instrumented vehicle over a 100 km (61 mi) primary highway circuit, accompanied by a licensed driving instructor having access to dual controls. The subject's task is to maintain a constant speed of 95 km/h (58 mi/h) and a steady lateral position between the delineated boundaries of the slower traffic lane. The vehicle speed and lateral position are continuously recorded. These signals are edited off line to remove data recorded during overtaking maneuvers or disturbances caused by roadway or traffic situations. The remaining data are then used to calculate means and standard deviations of lateral position and speed. Standard deviation of lateral position (SDLP in centimeters) is the primary outcome variable. SDLP is a measure of road tracking error or "weaving". The test duration is approximately 1 hour.

The Critical Tracking Test (CTT) measures the ability to control an unstable error signal in a first-order compensatory tracking task (Jex et al., 1966). Error is displayed as a horizontal deviation of a cursor from the midpoint on a horizontal, linear scale. Subjects use a joystick to null the error by returning the cursor to the midpoint. The frequency at which the subject loses the control is the critical frequency or λ_c in rad/s. The final score is determined from the average of all but the lowest and the highest scores in five trials.

The Divided Attention Task measures the ability to divide attention between two simultaneously performed tasks (Moskowitz, 1973). In the primary task the subject performs the same tracking task described above, yet at a constant level of difficulty set at 50% of his or her maximum capacity. In the secondary task the subject monitors 24 peripheral displays in which single digits change asynchronously at 5-second intervals. Subjects are instructed to remove their

foot from a pedal as rapidly as possible whenever the digit '2' appears. This signal occurs twice at every location, in random order, at intervals of 5 to 25 sec. Tracking error (in mm) and average reaction time (in ms) are the respective performance measures.

In the Stop Signal Task (Logan et al., 1984) the concept of inhibitory control is defined as the ability to stop a pending thought or action and to begin another. The paradigm consists of two concurrent tasks, i.e. a go task (primary task) and a stop task (secondary task). The go signals are the letters 'X' and 'O' presented one at a time in the center of a computer screen. Subjects are required to indicate as quickly as possible whether the letter presented is an 'X' or an 'O' by pressing one of two response buttons. The test consists of 336 trials. In 25% of the trials the go-signal is followed by a stop signal (a brief 1000 Hz tone) in which case subjects are required to withhold their response. Stop signals are presented after variable intervals dependent on the subject's go reaction time and ratio of successful and unsuccessful inhibitions. By continuously monitoring the subject's response the stop signal reaction time is calculated during the task. The dependent variables are go reaction time (in ms) and stop signal reaction time (in ms).

In the Word Learning Test (Rey, 1964) a sequence of 15 monosyllabic nouns is shown on a computer display at a rate of one per two seconds. Immediately thereafter the subject is required to verbally recall as many words as possible. The sequence is repeated on four more trials, and the highest separate trial score is the immediate recall score. After a delay of at least 30 minutes the subject is again required to recall as many words as possible without prompting. The total number of words correctly recalled is the delayed recall score. Finally, the subject is shown a sequence of 30 words on the computer display, including 15 words from the original set and 15 new words in random order. The subject has to indicate as quickly as possible whether a word originates from the original set or not by pressing a corresponding buttons. The number and speed of correct responses are recorded as the recognition score and the recognition reaction time (in ms), respectively.

CHAPTER 2

Body Sway was measured using the stabilometry method of the International Society of Posturography (Kapteyn et al., 1983). The subjects stands on a force platform for 60 sec with the feet open at an angle of approximately 30°, first with the eyes open and fixed on a target 2 meters away, and then with the eyes closed. The system (Electropostugraph, ELP, Brussels) calculates the momentary vector of force extending downward from the center of gravity of the body and its movement around the vertical axis over time, as illustrated in Boyle et al. (2008). Two related parameters are measured during both the eyes open and eyes closed recording epochs, i.e. the length of the vector's path (POS-L1 and POS-L2 in mm), and the area or surface circumscribed by the vector (POS-S1 and POS-S2, in mm²).

Subjective evaluations of mood, sedation and driving quality were assessed using a series of visual analogue scales (100 mm). The subject was instructed to rate their subjective feelings using a 16-item mood scale which provides three factor analytically defined summary scores for 'alertness', 'contentedness', and 'calmness' (Bond and Lader, 1974). The driving instructor rated each subject's driving quality and apparent sedation at the conclusion of each driving test, using two 100 mm visual analogue scales. Subjective feelings of sleepiness were rated by means of the Stanford sleepiness scale (Hoddes et al., 1972). The scale consists of 7 statements, describing stages of sleepiness ranging from feeling active and wide awake (1) to losing the struggle to remain awake and being nearly asleep (7). Subjective evaluation of sleep quality was assessed using the Groningen Sleep Quality Questionnaire (Mulder-Hajonides van der Meulen, 1981) and estimates of sleep onset latency and sleep duration.

Procedure

Subjects were individually trained to perform the driving and laboratory tests. One week before the first treatment period subjects slept in the same facilities as during treatment periods, to overcome possible sleep disturbances associated with sleeping in an unfamiliar environment. On the morning following this habituation night subjects rehearsed all tests including driving.

Treatment periods started in the evening of Day 1, when the subjects arrived at the site at approximately 20:00 hours, and lasted until Day 2, when they were transported home after the driving test, at approximately 11:15 hours. On arrival at the sleeping facility in each treatment period, subjects' eligibility was verified about adverse events and use of medication since their last visit, and measuring vital signs in supine position.

Subjects ingested their medication at 23:00 hours and retired to bed. They were awakened by telephone at 07:00 hours, i.e. 8 hours post-dose. At 07:45 hours (i.e. 8:45-09:30 hours post-dose) subjects performed the first session of laboratory tests comprising the following measures in fixed order: Immediate Recall of the Word Learning Test Body Sway, Critical Tracking Test, Divided Attention Task and first Delayed Recall of the Word Learning Test. In addition, subjects rated their sleep quality and feelings of alertness and sleepiness. From 09:00 hours until 10:00 hours, i.e. 10 to 11 hours after drug intake, the highway driving test was undertaken. Upon completion of the driving test the subjects returned to the testing facilities for a second test session, starting at approximately 11:45 hours after drug intake. After rating their subjective feelings and sleepiness, the subjects performed the Stop Signal Task, Critical Tracking Test, Divided Attention Task and the second Delayed Recall and Recognition part of the Word Learning Test.

Statistical analyses

Sample size was based on a power calculation for detecting a clinically relevant effect of 2.4 cm in the primary measure of this study, the SDLP. This change corresponds to the effects of alcohol on SDLP, while blood alcohol concentrations (BACs) are 0.5 g/L as measured in a previous study (Louwerens et al., 1987). Given a test-retest reliability of SDLP of at least $r=0.70$, a group of 18 subjects should permit detection of a mean change in SDLP of 2.0 cm, with a power of at least 90% and an α risk of 0.05.

The global model used in the repeated measures analysis of variance of all cognitive and psychomotor parameters included *subject*, *treatment*, and *session*. In case of a significant overall effect of treatment, a subsequent

CHAPTER 2

analysis for comparing separate drug treatments was conducted using three simple contrasts. All statistical analyses were done by using the Statistical Package for the Social Sciences (SPSS) statistical program (version 12.0.1 for Windows; SPSS, Chicago, IL).

RESULTS

A summary of the driving, cognitive and psychomotor tests is shown in table 1.

Missing data

Divided Attention Task data were incomplete for three subjects and Stop Signal Task data were incomplete for one subject due to technical problems. Only subjects with complete data sets entered the analysis of respective performance parameters.

Highway Driving Test

One driving test was terminated before scheduled completion because the driving instructor judged that it would be unsafe to continue. The terminated test was performed by a female subject after administration of zopiclone. The Standard Deviation of Lateral Position (SDLP) score was calculated from the data collected until termination of the ride.

Figure 1 presents mean \pm SE SDLP values recorded after every treatment. There was a significant overall treatment effect ($F_{2,16}=12.51$, $p<0.001$). Zopiclone significantly increased SDLP as compared to placebo (+2.0 cm, $p<0.002$) and temazepam ($p<0.001$). Effects of temazepam on SDLP were not significantly different from placebo.

Mean speed variability, reflected by the Standard Deviation of Speed (SDSP) differed significantly between treatments ($F_{2,16}=4.71$, $p=0.025$). SDSP was significantly increased following zopiclone as compared with temazepam ($p=0.011$). There were no significant differences between the hypnotics and placebo.

Critical Tracking Test

No overall treatment effect was found in tracking performance on either time of measurement.

Divided Attention Task

A significant overall treatment effect was found in tracking performance in the Divided Attention Task on the first test session ($F_{2,13}=4.08$, $p=0.042$), but not on the second test session. At 08:45 hours after administration tracking after zopiclone was significantly worse than after temazepam ($p=0.010$). There were no significant differences between drugs and placebo. No overall treatment effects were found on the target detection subtask.

Stop Signal Task

The ability to inhibit an ongoing action, as reflected by the stop signal reaction time (SSRT) was significantly different between treatments ($F_{2,15}=6.09$, $p=0.012$), whereas no significant differences between treatments were found in the go reaction time. SSRT was significantly increased after administration of zopiclone, as compared with placebo ($p=0.008$). Inhibitory control after temazepam administration did not differ from placebo or zopiclone.

Word Learning Test

No overall treatment differences were found for the immediate recall of verbally learned words.

For the delayed recall of the words, a significant treatment effect was revealed for both test sessions (8:45 hours post dose: $F_{2,16}=8.58$, $p=0.003$; 11:45 hours post dose: $F_{2,16}=6.75$, $p=0.007$). Delayed recall was significantly worse following zopiclone at both times of testing as compared to placebo ($p=0.008$ and $p=0.002$, respectively) and as compared to temazepam ($p=0.001$ and $p=0.017$, respectively). Temazepam had no significant effects on delayed recall.

There was a highly significant treatment effect on the number of correctly recognized words ($F_{2,16}=12.89$, $p<0.001$), which was due to a significantly lower

CHAPTER 2

recognition score after administration of zopiclone as compared with placebo ($p < 0.001$). No differences were found between temazepam and placebo and between the two treatment conditions. Reaction times to correctly recognized words also differed significantly between treatments ($F_{2,16} = 9.74$, $p = 0.002$). Compared with placebo, the subjects responded significantly slower after administration of both hypnotics (temazepam: $p = 0.003$; zopiclone: $p = 0.002$).

Body Sway

There was a significant treatment effect on body sway measured by vector surface with eyes open ($F_{2,16} = 4.19$, $p = 0.034$), but not measured with eyes closed or vector length. Sway surface, with eyes open was significantly increased by temazepam ($p = 0.013$) and zopiclone ($p = 0.015$), as compared to placebo.

Subjective evaluations

Subjects' ratings of sleepiness as measured by the Stanford Sleepiness Scale differed significantly between treatments during the first test session ($F_{2,16} = 4.47$, $p = 0.029$). Subjects felt more sleepy after administration of zopiclone than after temazepam ($p = 0.008$). This difference had disappeared on the second test session, i.e. 11:45 hours post dose. The effects of the drugs did not differ from placebo. There were no significant differences between treatments in alertness, calmness and contentedness as measured by Bond and Lader's mood scale.

The driving instructors rated the subjects' appearance of being sedated significantly different between the treatments ($F_{2,16} = 3.62$, $p = 0.05$). The subjects appeared significantly more sedated only following zopiclone ingestion compared with placebo ($p = 0.013$). The instructors did not judge the subjects' driving quality to be significantly different between treatments.

Subjective sleep quality

Subjective sleep quality was rated significantly different between treatments ($F_{2,16} = 7.91$, $p = 0.004$); the mean \pm SE number of complaints decreased significantly from 6.1 ± 1.2 after placebo to 3.0 ± 0.7 after zopiclone ($p = 0.011$).

and to 1.6 ± 0.3 after temazepam ($p < 0.001$). The difference in sleep complaints between the two hypnotics was significant ($p = 0.025$).

Further differences were found in estimations of time to sleep onset ($F_{2,16} = 6.73$, $p = 0.004$), total sleep time ($F_{2,16} = 5.88$, $p = 0.012$) and number of awakenings ($F_{2,16} = 11.12$, $p < 0.001$), but not in the time awake before rise. The mean \pm SE sleep onset time after placebo was 58 ± 13 minutes. This improved significantly after use of temazepam to 14 ± 2 minutes ($p = 0.004$), but not after zopiclone (29 ± 10 minutes). Similarly, total sleep time improved significantly ($p = 0.004$) only after temazepam (436 ± 9 minutes) and not after zopiclone (413 ± 15 minutes) as compared with placebo (373 ± 16 minutes). The mean \pm SE number of awakenings dropped significantly from 3.4 ± 0.6 after placebo to 1.5 ± 0.4 after temazepam ($p < 0.001$) and 1.1 ± 0.3 after zopiclone ($p < 0.001$).

Table 1. continued from p. 62

Test	Time after intake (h:m)	Mean (SE)	Overall effect				Simple contrast analysis			
			F	p	treatment	p	pla vs. tem	pla vs. zop	tem vs. zop	p
							Placebo	Temazepam	Zopiclone	
<i>Word Learning Test</i>										
Maximum IR	+8.45	13.2 (0.6)	NS				-	-	-	-
Delayed Recall 1	+8.45	10.9 (0.9)	8.58	0.003			NS	0.008	0.001	
Delayed Recall 2	+11.45	9.6 (0.9)	6.75	0.007			NS	0.002	0.017	
Recognition	+11.45	26.8 (0.7)	12.89	<0.001			NS	<0.001	NS	
Recognition RT	+11.45	842 (25)	9.74	0.002			0.003	0.002	NS	
<i>Body Sway</i>										
POS-L1 (mm)	+8.45	357 (12)	NS				-	-	-	
POS-S1 (mm ²)	+8.45	74 (7)	4.19	0.034			0.013	0.015	NS	
POS-L2 (mm)	+8.45	349 (8)	NS				-	-	-	
POS-S2 (mm ²)	+8.45	76 (6)	NS				-	-	-	
<i>Subjective Evaluations</i>										
Driving Quality	+10.0	69 (2)	NS				-	-	-	
Sedation	+10.0	10 (2)	3.62	0.050			NS	0.013	NS	

Table 1. continued from p. 63

Test	Time after intake (h:m)	Mean (SE)	Overall effect		treatment		Simple contrast analysis			
			F	p			pla vs. tem	pla vs. zop	tem vs. zop	p
Subjective Evaluations										
Alertness	+8.45	66 (5)								
	+11.45	72 (5)								
Contentedness	+8.45	70 (5)								
	+11.45	74 (6)								
Calmness	+8.45	71 (5)								
	+11.45	69 (5)								
Sleepiness	+8.45	2.0 (0.3)								
	+11.45	1.6 (0.2)								

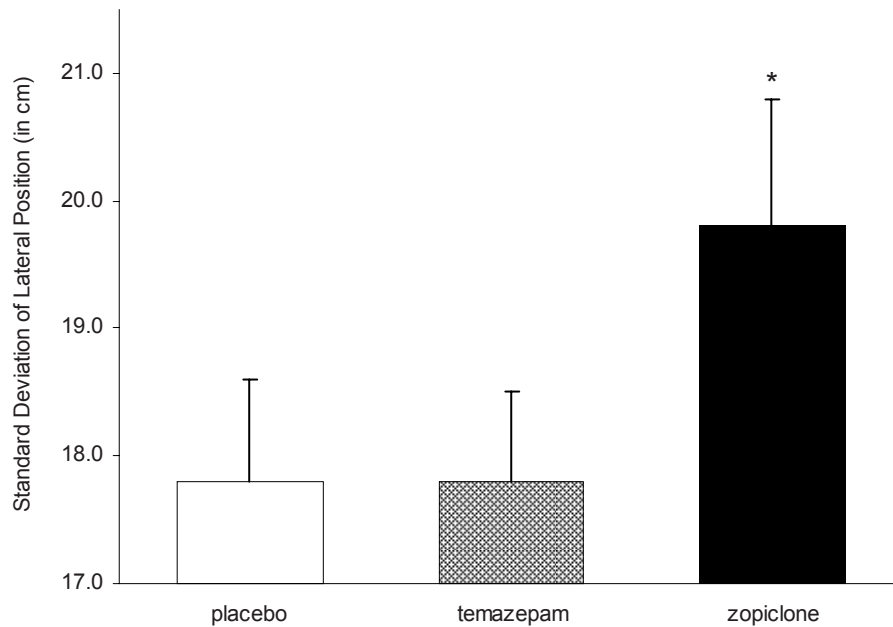


Figure 1. Mean (+SE) Standard Deviation of Lateral Position (SDLP) in each drug condition

* = significantly different from placebo ($p < 0.001$)

DISCUSSION

The present study is the first investigating the residual effects of hypnotics on actual driving performance in elderly drivers. Results show that a single oral dose of temazepam 20 mg does not affect driving performance in elderly individuals at 10 to 11 hours after bedtime administration. Zopiclone 7.5 mg, on the other hand, impairs driving significantly at 10 to 11 hours following intake as indicated by a significant rise in mean SDLP of +2.0 cm compared with placebo, which is almost comparable to the effects found for alcohol when blood alcohol concentrations were around 0.05% as assessed in a previous study (Louwerens et al., 1987). Furthermore, one driving test was stopped by the driving instructor, because the subject was too drowsy to continue safely after using zopiclone. In line with this, the driving instructors' evaluations showed that the

subjects appeared more sedated after using zopiclone than after placebo, yet they did not evaluate driving quality to differ between treatments.

The lack of residual effects on driving after use of temazepam 20 mg in our study is in line with results from previous studies in younger subjects using the same test (O'Hanlon and Volkerts, 1986, Riedel et al., 1988). O'Hanlon and Volkerts (1986) treated eleven insomniac women, aged between 26 and 38 years, with temazepam 20 mg, nitrazepam 10 mg and placebo for 8 nights and assessed the residual effects on driving after the first, third and seventh dose. Results showed that temazepam's effects were not significant throughout the week. Similarly, Riedel et al. (1988) found that temazepam 20 mg produced no residual effects on driving in shift workers (aged 24-50 years) as assessed 6.5 hours after the first and fifth dose. Our data therefore support that temazepam 20 mg is unlikely to produce residual effects on driving, even in healthy elderly drivers.

The significant residual effect of zopiclone 7.5 mg on driving in elderly drivers was expected, based on findings in younger individuals (Vermeeren et al., 1998, Vermeeren et al., 2002, Leufkens et al., in press). The increase in SDLP produced by zopiclone in the most recent study with young volunteers was +2.5 cm, while it was +2.0 cm in the present study with elderly (Leufkens et al., in press). Therefore, the present findings do not support the idea that the residual effects of hypnotics are more pronounced in older drivers.

A similar lack of age differences has been found for the effects of antidepressants on driving as assessed using the same test (van Laar et al., 1995). The impairing effects of the serotonin reuptake inhibitor nefazodone were found to be comparable in young (age 28-38 years) and elderly (age 60-72 years) healthy volunteers. It can therefore be concluded that studies in young volunteers are valid for predicting residual effects of hypnotics in healthy elderly drivers.

The results of the laboratory tests are in line with the effects on driving of both hypnotics. Effects of temazepam were marginal, only slowing response times in word recognition, and increasing postural sway as measured by one of the four parameters in the body sway test. Zopiclone, however, had clear

residual effects on memory as measured by delayed recall and speed and accuracy of recognition in the word learning test, inhibitory control in the stop signal task and postural stability in the body sway test. These effects are in agreement with findings from two previous studies using similar tests and procedures (Vermeeren et al., 2002, Leufkens et al., in press). Both drugs primarily affected postural sway when eyes were open, which may be due to the order of the measurements. Similar effects were shown previously in a study using the same procedures (Leufkens et al., in press).

Our results are not in line with those of a study by Hemmeter et al. (2000). These investigators found no significant effects of either temazepam 20 mg or zopiclone 7.5 mg on next day performance in 12 healthy elderly volunteers using a battery of laboratory tests, and found no significant effects of either temazepam 20 mg or zopiclone 7.5 mg. Although their results support our conclusions that elderly do not seem to be more sensitive to the residual effects of hypnotics than younger individuals, the complete lack of effects of zopiclone is rather unexpected and raises questions about the methodology used. This stresses the importance of the recommendation to include a control drug with moderately impairing effects to demonstrate sensitivity of the methods in studies assessing the effects of medicinal drugs on driving performance (ICADTS, 1999).

A limitation of our study with respect to generalization of the results to insomniac patients who drive may be the use of healthy volunteers. Residual effects of hypnotics are expected to be less severe in insomniacs than in healthy volunteers for two reasons. First, hypnotics are expected to improve daytime performance in insomniacs, as a result of improving sleep, which counteracts drug induced sedation. Secondly, most patients use these drugs repeatedly which may induce the development of tolerance (Bateson, 2002), and as a result, hypnotic-induced daytime impairment may become gradually less severe. With respect to the improving effects on sleep it should be noted that although the healthy elderly subjects in the present study considered themselves to be good sleepers, their scores on the Groningen Sleep Quality scale indicated that they had a clinically relevant number of sleep complaints

CHAPTER 2

during the placebo night, and they evaluated their sleep to be significantly improved following active hypnotic drugs. However, despite improved sleep, driving performance was impaired after zopiclone as compared to placebo. With respect to the development of tolerance, it should be noted that epidemiological studies have shown that the relative risk of becoming involved in a traffic accident is still significantly increased after one month of treatment, suggesting that tolerance to residual impairment was not complete (Neutel, 1998). Furthermore, patients using hypnotics on an as needed basis may not develop tolerance and may therefore remain susceptible to the sedative residual effects of hypnotics. Nevertheless, the validity of experimental studies with hypnotics in healthy volunteers for predicting the residual impairment on driving in patients with insomnia remains to be determined, preferably by studies in patients using the same drugs and procedures.

In conclusion, the results of the present study show that temazepam 20 mg is unlikely to produce residual effects on driving 10 hours or more after bedtime administration in healthy elderly aged 75 years or younger. Zopiclone 7.5 mg impairs driving in elderly at least until 11 hours after administration. The effects were comparable to those found in studies with healthy younger volunteers using the same methods, indicating that older drivers do not have an increased sensitivity to the residual effects of hypnotics.

REFERENCES

- Bateson, A. N. Basic pharmacologic mechanisms involved in benzodiazepine tolerance and withdrawal. *Curr Pharmaceut Des*, 2002, 8: 5-21.
- Bond, A., & Lader, M. The use of analogue scales in rating subjective feelings. *Br J Med Psychol*, 1974, 47: 211-218.
- Boyle J., Danjou P., Alexander R., Calder, N., Cargano, C., Agrawal, N., Fu, I., McCrea, J. B., & Murphy, M.G. Tolerability, pharmacokinetics and night-time effects on postural sway and critical flicker fusion of gaboxadol and zolpidem in elderly subjects. *Br J Clin Pharmacol*, 2008, 67:180-190.

- Busto, U. E., Sproule, B. A., Knight, K. & Herrmann, N. Use of prescription and nonprescription hypnotics in a Canadian elderly population. *Can J Clin Pharmacol*, 2001, 8: 213-221.
- Drake, C. L., Roehrs, T. & Roth, T. Insomnia causes, consequences, and therapeutics: an overview. *Depress Anxiety*, 2003, 18: 163-176.
- Glass, J., Lanctot, K. L., Herrmann, N., Sproule, B. A. & Busto, U. E. Sedative hypnotics in older people with insomnia: meta-analysis of risks and benefits. *BMJ Clin Res*, 2005, 331: 1169-1175.
- Hemmeter, U., Muller, M., Bischof, R., Annen, B. & Holsboer Trachsler, E. Effect of zopiclone and temazepam on sleep EEG parameters, psychomotor and memory functions in healthy elderly volunteers. *Psychopharmacol*, 2000, 147: 384-396.
- Hoddes, E., Dement, W. & Zarcone, V. The development and use of the Stanford sleepiness scale. *Psychophysiol*, 1972, 9: 150.
- ICADTS. Guidelines on experimental studies undertaken to determine a medicinal drug's effect on driving or skills related to driving. Cologne, Bundes Anstalt fuer Strassenwesen (BASt), 1999.
- Jex, H. R., McDonnell, J. D. & Phatak, A. V. A "critical" tracking task for man-machine research related to the operator's effective delay time. I. Theory and experiments with a first-order divergent controlled element. NASA CR-616. *NASA Contract Rep NASA CR*, 1966: 1-105.
- Kapteyn, T. S., Bles, W., Nijokiktijen, C. J., Kodde, L., Massen, C.H., & Mol, J. M. Standardization in platform stabilometry being part of posturography. *Agressol*, 1983, 24: 321-326.
- Kassam, A., Carter, B. & Patten, S. B. Sedative hypnotic use in Alberta. *Can J Psychiat*, 2006, 51: 287-294.
- Leufkens, T. R. M., Lund, J. S. & Vermeeren, A. Highway driving performance and cognitive functioning the morning after bedtime and middle-of-the-night use of gaboxadol, zopiclone and zolpidem. *J Sleep Res*, in press.
- Logan, G. D., Cowan, W. B. & Davis, K. A. On the ability to inhibit simple and choice reaction time responses: a model and a method. *J Exp Psychol Hum Percept Perform*, 1984, 10: 276-291.

CHAPTER 2

- Louwerens, J. W., Gloerich, A. B. M., Vries, D., G., Brookhuis, K. A. & O'Hanlon, J. F. The relationship between drivers' blood alcohol concentration (BAC) and actual driving performance during high speed travel. *Alcohol Drugs Traff Safe*, 1987, T86: 183-186.
- Moskowitz, H. Proceedings: Psychological tests and drugs. *Pharmakopsychiatrie, Neuro Psychopharmakol*, 1973, 6: 114-126.
- Mulder-Hajonides Van Der Meulen, W. R. E. H. *Measurement of subjective sleep quality*, Amsterdam, Elsevier, 1981.
- Neutel, I. Benzodiazepine-related traffic accidents in young and elderly drivers. *Hum Psychopharmacol Clin Exp*, 1998, 13: S115-S123.
- O'Hanlon, J. F. Driving performance under the influence of drugs: rationale for, and application of, a new test. *Br J Clin Pharmacol*, 1984, 18 Suppl 1: 121s-129s.
- O'Hanlon, J. F., Haak, T. W., Blaauw, G. J. & Riemersma, J. B. Diazepam impairs lateral position control in highway driving. *Science*, 1982, 217: 79-81.
- O'Hanlon, J. F. & Volkerts, E. R. Hypnotics and actual driving performance. *Acta Psychiat Scand. Supplementum*, 1986, 332: 95-104.
- Ramaekers, J. G. Antidepressants and driver impairment: empirical evidence from a standard on-the-road test. *J Clin Psychiat*, 2003, 64: 20-29.
- Ramaekers, J. G., Muntjewerff, N. D., Uiterwijk, M. M. C., Van Veggel, L. M. A., Patat, A., Durrieu, G., & O'Hanlon, J. F. A study of the pharmacodynamic interaction between befloxacitane and ethanol on performance and mood in healthy volunteers. *J Psychopharmacol*, 1996, 10: 288-294.
- Rey, A. *L'examen clinique en psychologie.*, Paris, Presses Universitaires de France, 1964.
- Riedel, W. J., Quasten, R., & O'Hanlon, J. F. Effects of midazolam triazolam and temazepam on shiftworkers' day-sleep and subsequent driving performance. *Psychopharmacol*, 1988, 96: 156S.
- Rosenberg, R. P. Sleep maintenance insomnia: strengths and weaknesses of current pharmacologic therapies. *Ann Clin Psychiat*, 2006, 18: 49-56.

- Theunissen, E. L., Vermeeren, A., Vuurman, E. F. P. M. & Ramaekers, J. G. Drugs, driving and traffic safety in allergic rhinitis. In Verster, J. C., Pandi-Perumal, S. R., Ramaekers, J. G. & De Gier, J. J. (Eds.) *Drugs, Driving and Traffic Safety*. Basel, Birkhauser, 2009.
- Van Laar, M. W., Van Willigenburg, A. P. & Volkerts, E. R. Acute and subchronic effects of nefazodone and imipramine on highway driving, cognitive functions, and daytime sleepiness in healthy adult and elderly subjects. *J Clin Psychopharmacol*, 1995, 15: 30-40.
- Vermeeren, A. Residual effects of hypnotics: epidemiology and clinical implications. *CNS Drugs*, 2004, 18: 297-328.
- Vermeeren, A., Danjou, P. E. & O'Hanlon, J. F. Residual effects of evening and middle-of-the-night administration of zaleplon 10 and 20 mg on memory and actual driving performance. *Hum Psychopharmacol*, 1998, 13: S98-S107.
- Vermeeren, A., Leufkens, T. R. M. & Verster, J. C. Effects of anxiolytics on driving. In Verster, J. C., Pandi-Perumal, S. R., Ramaekers, J. G. & De Gier, J. J. (Eds.) *Drugs, Driving and Traffic Safety*. Basel, Birkhauser, 2009.
- Vermeeren, A., O'Hanlon, J. F., Declerck, A. C., & Kho, L. Acute effects of zolpidem and flunitrazepam on sleep, memory and driving performance, compared to those of partial sleep deprivation and placebo. *Acta Ther*, 1995, 21: 47-64.
- Vermeeren, A., Riedel, W. J., Van Boxtel, M. P., Darwish, M., Paty, I. & Patat, A. Differential residual effects of zaleplon and zopiclone on actual driving: a comparison with a low dose of alcohol. *Sleep*, 2002, 25: 224-231.
- Verster, J. C., Volkerts, E. R., Schreuder, A. H., Eijken, E. J., Van Heuckelum, J. H., Veldhuijzen, D. S., Verbaten, M. N., Paty, I., Darwish, M., Danjou, P. & Patat, A. Residual effects of middle-of-the-night administration of zaleplon and zolpidem on driving ability, memory functions, and psychomotor performance. *J Clin Psychopharmacol*, 2002, 22: 576-583.

CHAPTER 2

- Volkerts, E. R. & O'Hanlon, J. F. Residu effecten van voorgeschreven hypnotica op de actuele rijprestatie (Residual effects of prescribed hypnotics on actual driving performance; Dutch with English summary and legends). *JDR J Drugther Res*, 1988, 13: 111-114.
- Woodward, M. Hypnosedatives in the elderly. *CNS Drugs*, 1999, 11: 263-279.

CHAPTER 3

Zopiclone's residual effects on actual driving performance in a standardized test: a pooled analysis of age and gender effects in four placebo controlled studies

Leufkens TRM, Vermeeren A.

ABSTRACT

In many European countries, Canada and Japan, the non-benzodiazepine zopiclone now is among the most frequently prescribed hypnotic drugs. This can be explained by the growing view among physicians that zopiclone is more effective and safer than conventional benzodiazepines. It has been shown, however, in four studies using similar procedures that zopiclone 7.5 mg produces moderate to severe impairment on driving performance. The present paper aims to review these studies and analyze the pooled data to determine whether the severity of effects is modified by the gender and age of the subjects.

Results show that zopiclone 7.5 mg has significant and clinically relevant impairing effects on driving performance in the morning, until 11 hours after bedtime ingestion. The effects do not differ between males and females and do not increase with age, at least until 75 years.

It is concluded that patients using an evening dose of zopiclone 7.5 mg should avoid activity in skilled work and participation in traffic the morning after intake. General practitioners' beliefs about the beneficial safety profile of zopiclone may need adjustment and patients using zopiclone 7.5 mg should be warned accordingly. In addition, there is no need to differentiate warnings about zopiclone's residual impairing effects depending on the gender of the patient.

INTRODUCTION

The prescription of newer hypnotics like zopiclone, zolpidem and zaleplon, has been steadily rising over the last years, whereas prescriptions of benzodiazepines have been falling (Dundar et al., 2004). In many European countries, Canada and Japan, the non-benzodiazepine zopiclone now is among the most frequently prescribed hypnotic drugs (Busto et al., 2001, Hajak et al., 2003, Kassam et al., 2006, Siriwardena et al., 2008, CVZ, 2008). This can be explained by the growing view among physician's that these newer hypnotics are more effective and safer than conventional benzodiazepines (Montplaisir et

al., 2003). A recent survey comparing primary care physicians' perceptions of benefits and risks of benzodiazepine and Z-drug use, found that Z-drugs were believed to be more effective than benzodiazepines in terms of patients feeling rested on waking, daytime functioning, and total sleep time (Siriwardena et al., 2006). They were also thought to be safer in terms of tolerance, dependence, residual daytime sedation, and road traffic accidents.

With respect to zopiclone's potential to produce residual sedation and to affect daytime functioning, several studies have been conducted, but the results were not consistent. This became apparent in the opposing conclusions of two reviews of zopiclone published in 1998 (Nicholson, 1998, Noble et al., 1998). In their review Noble et al. (1998) concluded that zopiclone 7.5 mg is unlikely to produce any significant residual clinical effects the morning after bedtime administration, whereas Nicholson (1998) concluded in his review that patients using zopiclone 7.5 mg should not participate in activities that involve skilled work and where impairment of performance could be a danger to themselves or others. Judging from current opinion and the number of citations, the review by Noble and colleagues has been most influential.

Explanations for the inconsistencies in experimental findings at that time were discussed by O'Hanlon (O'Hanlon, 1995). In his literature review of zopiclone's residual effects, he found that of the sixteen studies assessing residual effects of bedtime doses of zopiclone 7.5 mg on next day psychomotor performance, only four found significant impairment (Billiard et al., 1987, Lader and Denney, 1982, Nicholson and Stone, 1982, Volkerts and O'Hanlon, 1988). However, most studies failed to meet methodological standards for research on hypnotic drugs, i.e. use of standardized tests with predictive validity for real-life psychomotor performance, use of an active control drug or verum whose effects can be taken as an indication of test sensitivity, and use of designs with sufficient statistical power for detecting relevant effects (Angst et al., 1995).

The study by Volkerts and O'Hanlon (1988) was least troubled by these factors, and therefore most convincingly suggesting that zopiclone 7.5 mg can impair next day psychomotor performance. In that study 16 female insomniacs were administered zopiclone 7.5 mg and placebo at bedtime for two

consecutive nights according to a double-blind, cross-over design. Residual effects were measured in the morning and afternoon (at 10 and 16 hours, respectively) following the second dose using a one-hour standardized driving test over a 100 km primary highway circuit in normal traffic. Results showed that zopiclone significantly impaired driving performance, as measured by road tracking error, in the morning, but not in the afternoon. The magnitude of impairment in the morning was comparable to that found previously for alcohol when blood alcohol concentrations (BAC) were 0.5 mg/ml (Louwerens et al., 1987). It was therefore concluded that although the effect was significant, it was low in magnitude. Moreover the effect quickly disappeared thereafter, probably reflecting zopiclone's relatively short half-life of approximately 5 hours.

Since the findings of Volkerts and O'Hanlon (1988) seemed to be an exception, the study merited replication. By now, our group has conducted four additional studies assessing the residual effects of zopiclone 7.5 mg on driving using the same test and procedures, and all have confirmed the previous findings (Vermeeren et al., 1998, Vermeeren et al., 2002b, Leufkens et al., in press, Leufkens and Vermeeren, in press). All studies were conducted according to double blind, placebo controlled crossover designs, in healthy male and female volunteers. Three studies were conducted in young volunteers (Vermeeren et al., 1998, Vermeeren et al., 2002b, Leufkens et al., in press), and one in elderly drivers (Leufkens and Vermeeren, in press). Zopiclone 7.5 mg produced moderate to severe impairment of driving performance between 10 and 11 hours post-dose in all four studies.

The present paper aims to review these findings and analyze the pooled data to determine whether the severity of effects is modified by the gender and age of the subjects. The use of standardized procedures in all four studies allows comparison and combination of data for pooled analysis of age and gender effects, for which sample sizes in individual studies do not suffice (e.g. Olkin, 1995, Sambeth et al., 2007). Although women and elderly have been found more sensitive to effects of various drugs (Anderson, 2008, Greenblatt et al., 2004), epidemiological studies have found that risks for traffic accidents

associated with use of benzodiazepines increase most for young males (cf. Vermeeren, 2004).

METHODS AND MATERIALS

Studies

The driving data of the placebo and zopiclone 7.5 mg evening treatment periods from a total of four studies conducted at Maastricht University were included in this pooled analysis (Vermeeren et al., 1998, Vermeeren et al., 2002b, Leufkens et al., in press, Leufkens and Vermeeren, in press). All studies were conducted according to balanced double blind, crossover designs, including treatment conditions consisting of administration of single oral doses of zopiclone 7.5 mg and placebo at bedtime. The effects on driving were always measured the next morning, between 10 and 11 hours after administration, using a standardized highway driving test. Subject samples comprised healthy volunteers of both sexes in equal proportions, without complaints of insomnia. Subjects were young volunteers (age range 21 to 45 years) in three studies, and elderly volunteers (age range 55 to 75 years) in one study. Table 1 summarizes the treatment conditions and characteristics of the subject samples for each study.

Study 1 (Vermeeren et al., 1998) was designed to assess the residual effects of evening and middle of the night doses of zaleplon 10 mg and 20 mg as compared to those of zopiclone 7.5 mg and placebo. Subjects were 28 (14 female, 14 male) healthy young volunteers with a mean \pm SD age 31.2 \pm 5.7 years.

Study 2 (Vermeeren et al., 2002b) was designed to evaluate the residual effects of zopiclone 7.5 mg and zaleplon 10 mg administered at bedtime and to compare them with the effects of a low dose of alcohol. Thirty healthy young individuals (15 female, 15 male) with a mean \pm SD age of 31.6 \pm 6.9 years participated in a two-part cross-over study. Part 1 was conducted as a single-blind, 2-way cross-over design with afternoon administration of alcohol or alcohol-placebo drinks. Driving performance was assessed when blood alcohol

levels were just below the legal limit for driving, i.e. 0.5 mg/mL. Part 2 followed a double-blind, 3-way cross-over design. Treatment conditions were zopiclone 7.5 mg, zaleplon 10 mg and placebo administered at bedtime.

Study 3 (Leufkens et al., in press) was designed to assess the residual effects of evening and middle of the night doses of gaboxadol 15 mg as compared to those of evening doses of zopiclone 7.5 mg, middle of the night doses of zolpidem 10 mg and placebo. A total of 25 healthy young volunteers (12 female, 13 male; mean \pm SD age of 31.4 \pm 7.5 years) completed this 5-way cross over study.

Study 4 (Leufkens and Vermeeren, in press) was conducted to assess the residual effects of evening doses of zopiclone 7.5 mg, temazepam 20 mg and placebo in healthy elderly volunteers. Subjects were 18 (10 female, 8 male) healthy elderly drivers with a mean \pm SD age of 64.3 \pm 4.3 years.

Subjects

The complete data set contained 101 volunteers (51 females and 50 males) in the age range of 21 to 73 years. Participants needed to possess a valid driving license for at least three years, and have a driving experience over the preceding three years of at least 5000 km/year for the young volunteers and at least 3000 km/year for the older volunteers.

All subjects were screened by a medical history questionnaire, a physical examination including ECG, blood chemistry and hematology assessments and urinary tests for pregnancy and drugs of abuse. Common exclusion criteria in the studies were any history or current evidence of any clinically significant physical or mental disorders, alcoholism or drug abuse; acute illness; use of systemic medication except oral contraceptives; use of any psychotropic drug; blood donation or participation in any other clinical trial within the previous three months; consumption of more than 6 beverages containing caffeine per day, use of more than 10 cigarettes per day, and drinking more than 21 alcohol containing beverages per week.

Table 1. Summary of the study designs of the four studies included in the pooled analysis. All studies were conducted following a double-blind, cross-over design

Study Treatments		Subjects	Age	Weight	Duration of	Annual	Reference
		N	Mean (SD), range in years	Mean (SD) by sex (f,m) in kg	Drivers License Mean (SD) by sex (f,m) in years	Mileage Mean (SD) by sex (f,m) in km/y	
1	<i>evening and middle of the night doses of</i> zaleplon 10 mg; zaleplon 20 mg; zopiclone 7.5 mg; placebo	14 females 14 males	31.2 (5.7) 23-40	66.1 (6.7) 78.7 (14.6)	11.1 (5.7) 11.1 (5.1)	12686 (4584) 23214 (17660)	Vermeeren et al. (1998)
2	<i>evening doses of</i> zaleplon 10 mg; zopiclone 7.5 mg; placebo	15 females 15 males	31.6 (6.9) 21-45	60.6 (6.1) 80.2 (10.9)	10.2 (7.0) 13.3 (6.9)	14600 (10614) 23800 (21415)	Vermeeren et al. (2002b)
3	<i>evening doses of</i> gaboxadol 15 mg; zopiclone 7.5 mg; placebo <i>middle of the night doses of</i> gaboxadol 15 mg; zolpidem 10 mg; placebo	12 females 13 males	31.4 (7.5) 22-44	66.8 (6.7) 77.7 (9.3)	11.2 (8.4) 12.1 (5.6)	13167 (13704) 15808 (6600)	Leufkens et al. (in press)
4	<i>evening doses of</i> temazepam 20 mg; zopiclone 7.5 mg; placebo	10 females 8 males	64.3 (4.4) 56-73	64.8 (5.6) 77.0 (4.9)	34.2 (9.9) 43.9 (4.8)	8258 (4207) 11563 (4640)	Leufkens & Vermeeren (in press)

CHAPTER 3

All studies were conducted in accordance with the code of ethics on human experimentation established by the World Medical Association's Declaration of Helsinki (1964) and its subsequent amendments. The protocols were approved by the medical ethics committee of Maastricht University and University Hospital of Maastricht. Subjects signed a written informed consent prior to any study-related assessments.

Procedure

Subjects were individually trained to perform the driving test. One week before the first treatment period subjects slept in the same facilities as during treatment periods to overcome possible sleep disturbances associated with sleeping in an unfamiliar environment. On the morning following this habituation night subjects rehearsed all tests and procedures including the driving test.

During treatment periods zopiclone 7.5 mg and placebo were orally administered at bedtime. Subjects were awakened after 8 hours time in bed and served a light breakfast without caffeine. Next, they conducted a battery of various psychometric tests. The driving test was always conducted between 10 and 11 hrs following bedtime administration.

Highway driving test

The driving test used in all studies was developed and standardized by O'Hanlon and colleagues in the early 1980's (O'Hanlon, 1984). In this test the subject operates a specially instrumented vehicle over a 100 km (61 mi) primary highway circuit in normal traffic, accompanied by a licensed driving instructor having access to dual controls. The subject's task is to maintain a constant speed of 95 km/h (58 mi/h) and a steady lateral position between the delineated boundaries of the slower traffic lane. Test duration is approximately one hour during which the vehicle's speed and lateral position are continuously recorded. These signals are edited off line to remove data recorded during overtaking maneuvers or disturbances caused by roadway or traffic situations. The remaining data are then used to calculate means and standard deviations of lateral position and speed. The pooled lateral position variance is calculated,

and its square root, the mean-adjusted standard deviation of lateral position (SDLP in centimeters) is taken as the primary outcome variable. SDLP is an integrated measure of road tracking error or “weaving”. It is an extremely reliable index (test-retest $r = 0.70$ to 0.90) of individual driving performance and has proven sensitive to many sedating drugs (O'Hanlon and Ramaekers, 1995, O'Hanlon et al., 1995, Ramaekers, 2003, Vermeeren, 2004, Verster, 2005, Leufkens et al., 2007). The test was calibrated for the effects of alcohol in a closed circuit study wherein 24 social drinkers were tested sober and after controlled drinking to raise blood alcohol concentrations in steps of 0.3 g/L to a maximum of 1.2 g/L (Louwerens et al., 1987). In line with the relation between BAC and accident risk as estimated in a large epidemiological study by Borkenstein and associates (Borkenstein et al., 1974), the relation between BAC and SDLP was shown to be an exponential function. Based on this relation BACs of 0.5, 0.8 and 1.0 g/L were associated with mean changes in SDLP of 2.4, 4.2 and 5.1 cm. Standard deviation of speed (SDSP in km/h) is measured as a secondary outcome variable and is an index of subjects' ability to maintain a constant speed.

Statistical analysis

Statistical analyses were performed using zopiclone-placebo difference scores in SDLP and SDSP as dependent variables (i.e. Δ SDLP and Δ SDSP, respectively). Δ SDLP and Δ SDSP were analyzed separately using 2-way ANOVAs with *Study* and *Gender* as fixed between subject factors. Significant main effects of *Study* were further analyzed using six simple contrasts between the studies change scores in elderly and young volunteers, using Bonferroni correction to adjust for six comparisons.

In order to determine which subject characteristic best predicted zopiclone's effect on driving, a step-wise regression analysis was used with Δ SDLP as dependent and sex, age, body weight, years of driving experience and annual mileage as predictors. The best predictors were used as covariates in a subsequent analysis of co-variance, to determine whether they could account for any Study or Gender differences.

To compare residual effects on SDLP and SDSP, correlations (Pearson r) and effect sizes (Dunlap's d , Dunlap et al., 1996) were calculated for studies and sexes separately, and for the total group.

RESULTS

Subjects

There were no significant differences between studies with respect to gender composition, body weight and average annual mileage of the subjects (Table 1). Subjects in study 4 were older and had, as can be expected, significantly more years of driving experience compared to the other studies (p 's <0.001). Overall, males differed from females in terms of body size (height and weight, p 's <0.001), and in terms of driving experience. They had more years of driving experience ($p=0.016$), and drove more kilometers per year ($p=0.015$).

Tests terminated prematurely

A total of four driving tests were terminated prematurely due to excessive drowsiness. All four tests were conducted after use of zopiclone. Two tests were stopped before scheduled completion in study 1: one by the driving instructor and one at the subject's request. Furthermore, the driving instructors stopped one test in study 2 and one in the study 4. SDLP scores for these tests were calculated from the data collected until termination and included in the statistical analyses.

Standard Deviation of Lateral Position

Figure 1 shows the individual and average SDLP scores after administration of placebo and zopiclone 7.5 mg for each study separately.

As reported in the original publications, the mean increases in SDLP following use of zopiclone as compared to placebo were significant in each study, varying from +1.94 cm in study 4 with elderly to +4.88 cm in study 1 with young volunteers. The overall mean (SD) increase in SDLP following use of zopiclone

as compared to placebo was +3.33 (3.42) cm, which is highly significant ($F_{1,93}=87.96$, $p<0.0001$). Analysis showed an overall difference in Δ SDLP between studies ($F_{3,93}=3.69$, $p=0.015$), which was due to a significantly smaller Δ SDLP in study 4 as compared to study 1 ($p=0.025$). There was no overall difference in Δ SDLP between males and females (+3.17 vs +3.49 cm, respectively; $F<1$) or a Gender by Study interaction.

Regression analysis of Δ SDLP with sex, age, body weight, years of driving, annual mileage as independent variables, revealed that only age ($F_{1,99}=5.7$, $p=0.019$) and years of driving ($F_{1,99}=8.2$, $p=0.005$) predicted Δ SDLP, with beta-coefficient of -0.23 and -0.27, and adjusted R^2 of 5% and 7%, respectively (figure 2).

Years of driving experience was highly correlated with age ($r=0.95$). Inclusion of these variables as co-variables in the analysis of differences between studies and sexes had no effects on the absence of Gender differences, but reduced the differences between studies. Study effects were no longer significant after correction for age ($F_{3,92}=2.29$, $p=0.084$) or years of driving experience ($F_{3,92}=2.33$, $p=0.079$).

Standard Deviation of Speed

The ability to keep a constant speed, as measured by Standard Deviation of Speed (SDSP) differed significantly between placebo and zopiclone ($F_{1,93}=17.86$, $p<0.0001$). Overall, the variability in speed was increased by 0.17 km/h after use of zopiclone. Zopiclone's effects on SDSP did not differ between studies and sexes (F 's<1.).

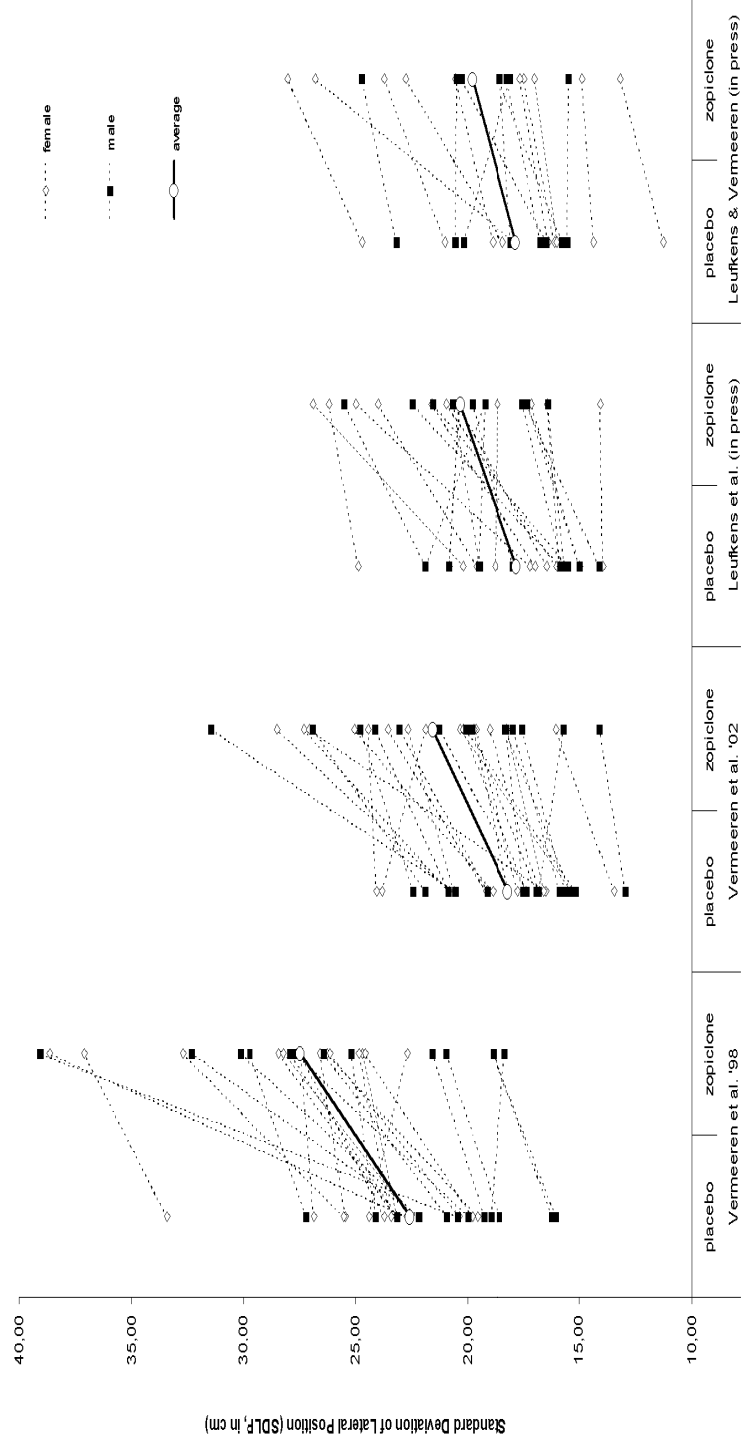


Figure 1. Individual SDLP scores for each study separately, including the average SDLP

Effect sizes

Table 2 shows the effect sizes of changes in SDLP and SDSP for the studies and males and females.

Effect sizes on SDLP were large, with a mean of 0.67 and ranging from 0.50 in study 4 with elderly to 0.96 in study 1 with young volunteers. The overall effect size on SDSP (0.35) was smaller than on SDLP, ranging from 0.30 in study 3 to 0.73 in study 4. Effect sizes on SDLP were slightly smaller for males than for females, whereas effect sizes on SDSP were slightly larger for males than for females.

Correlations

The overall correlation between Δ SDLP and Δ SDSP was 0.41 ($p < 0.001$), and ranged between 0.30 (n.s.) in study 3 and 0.73 ($p < 0.01$) in study 4 (table 2).

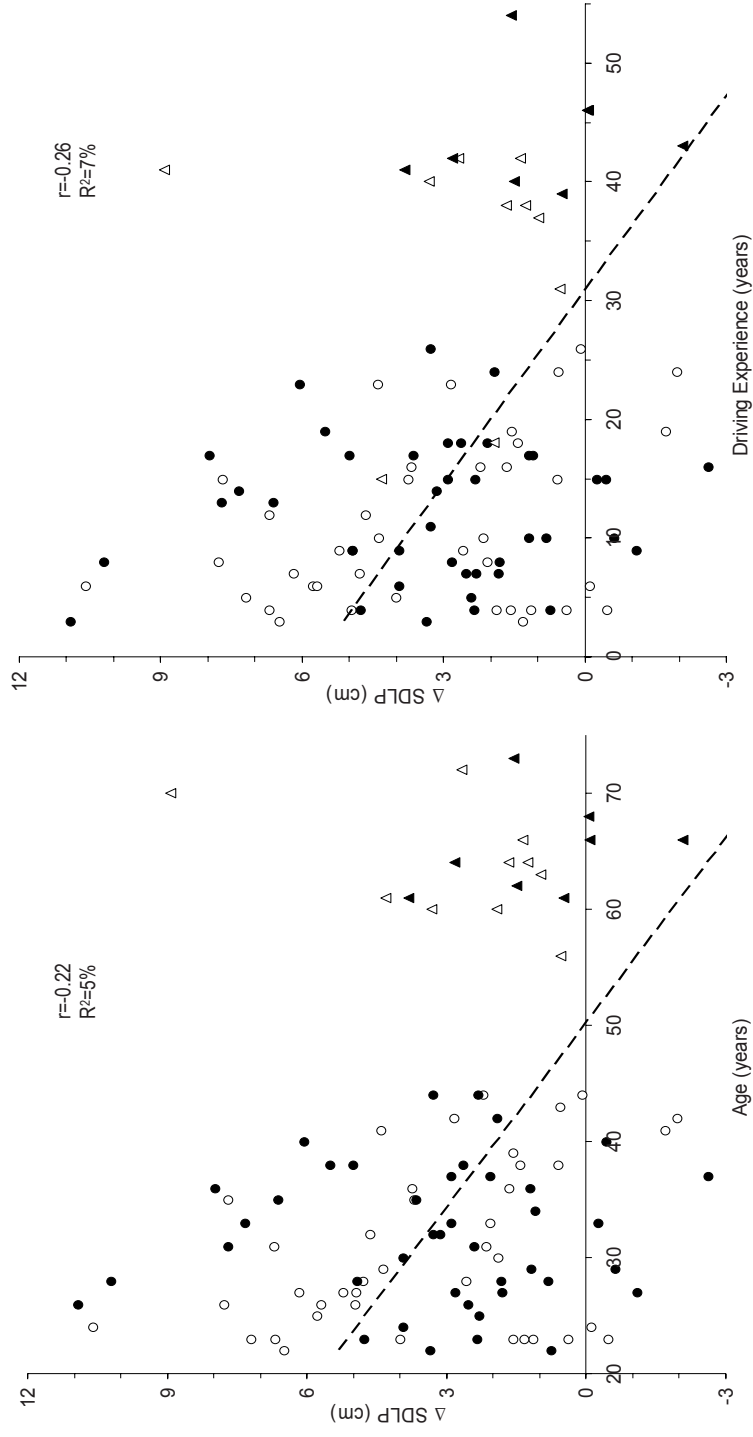


Figure 2. Regression line and individual changes in SDLP after use of zopiclone as compared to placebo as a function of age and driving experience. Symbols indicate young females (\circ , open circles), young males (\bullet , closed circles), elderly females (Δ , open triangles), and elderly males (\blacktriangle closed triangles)

RESIDUAL EFFECTS OF ZOPICLONE: A POOLED ANALYSIS

Table 2. Mean (SD) change scores (Δ), effect sizes and correlations between changes in SDLP and SDSP for each study and gender separately, and overall

	N	Tests terminated prematurely # (% of N)	Δ SDLP Mean (SD) in cm	Δ SDLP Effect size Dunlap's d	Δ SDSP Mean (SD) in km/h	Δ SDSP Effect size Dunlap's d	Correlation Δ SDLP – Δ SDSP Pearson's r
Vermeeren et al. (1998)	28	2 (7.1%)	4.88 (4.50)	0.96	0.15 (0.38)	0.35	0.58
Vermeeren et al. (2002b)	30	1 (3.3%)	3.38 (2.88)	0.89	0.11 (0.39)	0.24	0.34
Leufkens et al. (in press)	25	0	2.53 (2.65)	0.82	0.25 (0.30)	0.54	0.30
Leufkens & Vermeeren (in press)	18	1 (5.5%)	1.94 (2.32)	0.50	0.21 (0.59)	0.37	0.73
Females	51	3 (5.9%)	3.49 (3.27)	0.70	0.16 (0.45)	0.30	0.51
Males	50	1 (2.0%)	3.17 (3.59)	0.62	0.19 (0.37)	0.41	0.31
Overall	101	4 (4.0%)	3.33 (3.42)	0.67	0.17 (0.41)	0.35	0.41

DISCUSSION

This paper was intended to review the residual effects of zopiclone 7.5 mg on driving performance as measured by a standardized on-the-road driving test in normal traffic in four separate placebo-controlled double-blind crossover studies using the same procedures. Data from 101 subjects participating in these studies were pooled to provide a more reliable estimate of the magnitude and severity of zopiclone's residual effects and to determine whether these effects depend on age, gender, weight or driving experience of the subjects.

Results show that zopiclone 7.5 mg has significant, and most importantly, clinically relevant impairing effects on driving performance in the morning, until 11 hours after bedtime ingestion. Zopiclone impaired subjects' control over the vehicle's lateral position on the road (i.e. weaving) and driving speed. Weaving as measured by SDLP increased on average by 3.3 cm, which represents a moderate to large effect size (Dunlap's $d = 0.67$). Compared to the effects of alcohol in the same test (Louwerens et al., 1987), a 3.3 cm mean increase in SDLP is comparable to effects of a mean blood alcohol concentration (BAC) between 0.5 and 0.8 mg/ml, which is associated with a two to three fold increase in the risk of becoming involved in a traffic accidents (Krüger and Vollrath, 2004). According to the International Council on Alcohol Drugs and Traffic Safety (ICADTS) such effects can be classified as moderately severe impairment of driving performance (Wolschrijn et al., 1991). Patients using zopiclone 7.5 mg at bedtime should be warned therefore not to operate heavy machinery or engage in car driving the next morning until at least 11 hours after ingestion.

Zopiclone's effects on variance in driving speed (SDSP) were also significant, but considerably less pronounced as compared to those on SDLP in terms of effect sizes (Dunlap's d of 0.35 vs 0.67, respectively). The overall correlation between zopiclone's effects on SDLP and SDSP is moderate ($r=0.41$). These results indicate that subjects' control of the vehicle's lateral position is most sensitive to the residual effects of zopiclone. This is supported by results from studies by Bocca et al. (Bocca et al., 1999) and Berthelon et al. (Berthelon et al., 2003, Berthelon et al., 2008) using various scenarios in driving simulators for assessing the residual effects of zopiclone 7.5 mg. These investigators found that zopiclone significantly impaired control of lateral position, but not control of speed (Bocca et al., 1999), collision anticipation (Berthelon et al., 2003), and processing of visual information in a driving context (Berthelon et al., 2008). Moreover, a recent epidemiological study of unsafe driving actions in crash involved drivers showed that "failure to stay in proper lane/running of road" was the most frequently reported unsafe driving action by benzodiazepine

users (Dubois et al., 2008). This supports the validity of SDLP for measuring safe driving and its impairment by sedating drugs like benzodiazepines.

Another objective of this pooled analysis was to determine whether there are significant age and gender differences in the severity of residual effects of zopiclone on driving performance. Analysis of the pooled data revealed no gender differences in the effects of zopiclone on SDLP and SDSP. This is in line with findings by Greenblatt et al. (2000) reporting a similar lack of gender differences after administration of hypnotics in a study comparing the effects of triazolam and zolpidem on psychomotor performance and memory (Greenblatt et al., 2000). On the one hand, alcohol and some medicinal drugs have been found to produce larger pharmacological responses in females than in males (Anderson, 2008, Vermeeren et al., 2002a), which can usually be explained by their lower body weight. On the other hand, it has been found that total clearance of drugs metabolized by the cytochrome P450 (CYP) 3A4 system, like zopiclone, is slightly faster in women compared to men, although results were not consistent (Greenblatt et al., 2004, Schwartz, 2003). The combination of these effects may explain the lack of gender differences in the residual effects of zopiclone. It can be concluded that there is no need to differentiate warnings about zopiclone's residual impairing effects depending on the gender of the patient.

Contrary to expectations, the effect on driving in our older sample was generally less than that found in studies with younger volunteers. The difference was significant for only one out of three studies though (Vermeeren et al., 1998). Several factors may have contributed to this finding. Increased drug effects in elderly are usually due to age related reductions in body size and body fat, reduced clearance, and altered baseline performance (Greenblatt et al., 2004). In our studies there were no differences in body weight between subject samples. Second, our older subjects were all younger than 75 years and selected to be healthy and having normal liver and kidney function. Age related reductions in drug clearance are perhaps more likely to occur in elderly over 75 years. Third, our elderly subjects had significantly more years of driving

experience and were still regular drivers. Their driving performance after placebo was generally similar or even better in terms of SDLP compared to younger drivers. In fact, years of driving experience seemed a slightly better predictor of zopiclone's effects than age. Both predicted only 5 to 7% of the variation in effects, however, indicating that relation is weak.

Although the protective effects of age or driving experience seemed low, the results are supported by other experimental and epidemiological studies suggesting that younger and less experience drivers are more sensitive to drug effects. A number of epidemiological studies have found that risks for traffic accidents associated with use of benzodiazepines increase most for young males (cf. Vermeeren 2004). In addition, a recent on-the-road driving study showed that the effects of low doses of alcohol on weaving were more severe in novice drivers than in experienced drivers (Vuurman and Giorgetti, 2009). Novice drivers are thought to make use of more cognitive resources than experienced drivers. The sedative properties of hypnotics may influence more cognitive skills in relatively inexperienced drivers and, as a consequence, impair performance in a larger extent than in experienced drivers. Age related increases in driving experience may therefore have protective effects on drug induced driving impairment.

Finally it should be mentioned that, although the impairing effects of zopiclone on driving performance are highly significant, they do not appear to be noticed by the subjects. In all four studies subjects were asked to indicate their subjective alertness in the morning after evening administration using a visual analogue scale (Bond and Lader, 1974). Subjects did not report any differences in feelings of alertness between placebo and zopiclone administration. In the Vermeeren et al. (2002b) study subjects were, however, able to detect the impairing effects of alcohol on their alertness while blood alcohol concentrations were 0.4 mg/mL. In contrast, the effects on driving performance after alcohol were less impairing than the effects of zopiclone 7.5 mg, showing that the subjects' alertness does not correctly predict their driving performance. This stresses the importance of providing clear and comprehensive information about the potentially hazardous effects of zopiclone

on driving performance by general practitioners and pharmacists to their patients.

In conclusion, the results of the study show that zopiclone 7.5 mg has significant impairing effects on driving performance at least until 11 hours after hypnotic intake. The effects do not differ between males and females and do not increase with age, at least until 75 years. The results fully support recommendations by Nicholson (Nicholson, 1998) that patients using an evening dose of zopiclone 7.5 mg should avoid activity in skilled work and participation in traffic the morning after intake. General practitioners' beliefs about the beneficial safety profile of zopiclone may need adjustment and patients using zopiclone 7.5 mg should be warned accordingly.

REFERENCES

- Anderson, G. D. Gender differences in pharmacological response. *Internat Rev Neurobiol*, 2008, 83: 1-10.
- Angst, J., Borbely, A., Engel, R. R., Ferner, U., Gaszner, P., Hippius, H., Lader, M., Lingjaerde, O., Ruther, E., Rzwuska, M., Saletu, B., Sedvall, G., Soldatos, C., Stefanis, C. N. & Stoll, K. D. Report on the sixth consensus conference on the methodology of clinical trials with hypnotic drugs. *Pharmacopsychiat*, 1995, 28: 2-7.
- Berthelon, C., Bocca, M. L., Denise, P. & Pottier, A. Do zopiclone, zolpidem and flunitrazepam have residual effects on simulated task of collision anticipation? *J Psychopharmacol*, 2003, 17: 324-331.
- Berthelon, C., De Longcamp, A., Coquerel, A. & Denise, P. Residual effects of zolpidem, zopiclone and flunitrazepam on the processing of visual information in driving context. *Rev Eur Psycholog Appl*, 2008, 58: 111-116.
- Billiard, M., Besset, A., De Lustrac, C. & Brissaud, L. Dose-response effects of zopiclone on night sleep and on nighttime and daytime functioning. *Sleep*, 1987, 10 Suppl 1: 27-34.

CHAPTER 3

- Bocca, M. L., Le Doze, F., Etard, O., Pottier, M., L'Hoste, J. & Denise, P. Residual effect of zolpidem 10 mg and zopiclone 7.5 mg versus flunitrazepam 1 mg and placebo on driving performance and ocular saccades. *Psychopharmacol*, 1999, 143: 373-379.
- Bond, A., & Lader, M. The use of analogue scales in rating subjective feelings. *Br J Med Psychol*, 1974, 47: 211-218.
- Borkenstein, R. F., Crowther, F. R., Shumate, R. P., Ziel, W. B. & Zylman, R. The role of drinking driver in traffic accidents: the Grand Rapids Study. *Blutalkohol*, 1974, 11: 1-131.
- Busto, U. E., Sproule, B. A., Knight, K. & Herrmann, N. Use of prescription and nonprescription hypnotics in a Canadian elderly population. *Can J Clin Pharmacol*, 2001, 8: 213-221.
- College voor Zorgverzekeringen (CVZ), 2008. Aantal voorschriften 2003-2007 voor ATC-subgroep N05C: Hypnotica en sedativa (Number of prescriptions of ATC-subgroup N05C: Hypnotics and sedatives). Genees- en hulpmiddelen Informatie Project (GIP)
- Dubois, S., Bedard, M. & Weaver, B. The impact of benzodiazepines on safe driving. *Traff Inj Prev*, 2008, 9: 404-413.
- Dundar, Y., Boland, A., Strobl, J., Dodd, S., Haycox, A., Bagust, A., Bogg, J., Dickson, R. & Walley, T. Newer hypnotic drugs for the short-term management of insomnia: a systematic review and economic evaluation. *Health Technol Assess*, 2004, 8: 1-125.
- Dunlap, W. P., Cortina, J. M., Vaslow, J. B. & Burke, M. J. Meta-analysis of experiments with matched groups or repeated measures designs *Psychol Meth*, 1996, 1: 170-177.
- Greenblatt, D. J., Harmatz, J. S., Von Moltke, L. L., Wright, C. E., Durol, A. L., Harrel Joseph, L. M. & Shader, R. I. Comparative kinetics and response to the benzodiazepine agonists triazolam and zolpidem: evaluation of sex-dependent differences. *J Pharmacol Exp Ther*, 2000, 293: 435-443.
- Greenblatt, D. J., Harmatz, J. S., Von Moltke, L. L., Wright, C. E. & Shader, R. I. Age and gender effects on the pharmacokinetics and

- pharmacodynamics of triazolam, a cytochrome P450 3A substrate. *Clin Pharmacol Ther*, 2004, 76: 467-479.
- Hajak, G., Muller, W. E., Wittchen, H. U., Pittrow, D. & Kirch, W. Abuse and dependence potential for the non-benzodiazepine hypnotics zolpidem and zopiclone: a review of case reports and epidemiological data. *Addiction*, 2003, 98: 1371-1378.
- Kassam, A., Carter, B. & Patten, S. B. Sedative hypnotic use in Alberta. *Can J Psychiat*, 2006, 51: 287-294.
- Krüger, H. P. & Vollrath, M. The alcohol-related accident risk in Germany: procedure, methods and results. *Acc Anal Prev*, 2004, 36: 125-133.
- Lader, M. & Denney, S. C. A double-blind study to establish the residual effects of zopiclone on performance in healthy volunteers. *Internat Pharmacopsychiat*, 1982, 17: 98-108.
- Leufkens, T. R. M., Vermeeren, A., Smink, B. E., Van Ruitenbeek, P. & Ramaekers, J. G. Cognitive, psychomotor and actual driving performance in healthy volunteers after immediate and extended release formulations of alprazolam 1 mg. *Psychopharmacol*, 2007, 191: 951-959.
- Leufkens, T. R. M., Lund, J. S. & Vermeeren, A. Highway driving performance and cognitive functioning the morning after bedtime and middle-of-the-night use of gaboxadol, zopiclone and zolpidem. *J Sleep Res*, in press.
- Leufkens, T. R. M. & Vermeeren, A. Highway driving in elderly the morning after bedtime use of hypnotics: a comparison between temazepam 20 mg, zopiclone 7.5 mg and placebo. *J Clin Psychopharmacol*, in press.
- Louwerens, J. W., Gloerich, A. B. M., Vries, D., G., Brookhuis, K. A. & O'Hanlon, J. F. The relationship between drivers' blood alcohol concentration (BAC) and actual driving performance during high speed travel. *Alcohol Drugs Traffic Safe*, 1987, T86: 183-186.
- Montplaisir, J., Hawa, R., Moller, H., Morin, C., Fortin, M., Matte, J., Reinish, L. & Shapiro, C. M. Zopiclone and zaleplon vs benzodiazepines in the treatment of insomnia: Canadian consensus statement. *Hum Psychopharmacol*, 2003, 18: 29-38.

CHAPTER 3

- Nicholson, A. N. Residual sequelae of zopiclone. *Rev Contemp Pharmacother*, 1998, 9: 123-129.
- Nicholson, A. N. & Stone, B. M. Zopiclone: sleep and performance studies in healthy man. *Internat Psychopharmacol*, 1982, 17: 92-97.
- Noble, S., Langtry, H. D. & Lamb, H. M. Zopiclone. An update of its pharmacology, clinical efficacy and tolerability in the treatment of insomnia. *Drugs*, 1998, 55: 277-302.
- O'Hanlon, J. F. Driving performance under the influence of drugs: rationale for, and application of, a new test. *Br J Clin Pharmacol*, 1984, 18 Suppl 1: 121s-129s.
- O'Hanlon, J. F. Zopiclone's residual effects on psychomotor and information processing skills involved in complex tasks such as car driving: a critical review. *Eur Psychiat*, 1995, 10: 137s-143s.
- O'Hanlon, J. F. & Ramaekers, J. G. Antihistamine effects on actual driving performance in a standard test: a summary of Dutch experience, 1989-94. *Allergy*, 1995, 50: 234-242.
- O'Hanlon, J. F., Vermeeren, A., Uiterwijk, M. M., Van Veggel, L. M. & Swijgman, H. F. Anxiolytics' effects on the actual driving performance of patients and healthy volunteers in a standardized test. An integration of three studies. *Neuropsychobiol*, 1995, 31: 81-88.
- Olkin, I. Meta-analysis: reconciling the results of independent studies. *Stat Med*, 1995, 14: 457-472.
- Ramaekers, J. G. Antidepressants and driver impairment: empirical evidence from a standard on-the-road test. *J Clin Psychiat*, 2003, 64: 20-29.
- Sambeth, A., Blokland, A., Harmer, C. J., Kilkens, T. O. C., Nathan, P. J., Porter, R. J., Schmitt, J. A. J., Scholtissen, B., Sobczak, S., Young, A. H. & Riedel, W. J. Sex differences in the effect of acute tryptophan depletion on declarative episodic memory: A pooled analysis of nine studies. *Neurosc Biobehav Rev*, 2007, 31: 516-529.
- Schwartz, J. B. The influence of sex on pharmacokinetics. *Clin Pharmacokinet*, 2003, 42: 107-121.

- Siriwardena, A. N., Qureshi, M. Z., Dyas, J. V., Middleton, H. & Orner, R. Magic bullets for insomnia? Patients' use and experiences of newer (Z drugs) versus older (benzodiazepine) hypnotics for sleep problems in primary care. *Br J Gen Pract*, 2008, 58: 417-422.
- Siriwardena, A. N., Qureshi, Z., Gibson, S., Collier, S. & Latham, M. GPs' attitudes to benzodiazepine and 'Z-drug' prescribing: a barrier to implementation of evidence and guidance on hypnotics. *Br J Gen Pract*, 2006, 56: 964-967.
- Vermeeren, A. Residual effects of hypnotics: epidemiology and clinical implications. *CNS Drugs*, 2004, 18: 297-328.
- Vermeeren, A., Danjou, P. E. & O'Hanlon, J. F. Residual effects of evening and middle-of-the-night administration of zaleplon 10 and 20 mg on memory and actual driving performance. *Hum Psychopharmacol*, 1998, 13: S98-S107.
- Vermeeren, A., Ramaekers, J. G. & O'Hanlon, J. F. Effects of emedastine and cetirizine, alone and with alcohol, on actual driving of males and females. *J Psychopharmacol*, 2002a, 16: 57-64.
- Vermeeren, A., Riedel, W. J., Van Boxtel, M. P., Darwish, M., Paty, I. & Patat, A. Differential residual effects of zaleplon and zopiclone on actual driving: a comparison with a low dose of alcohol. *Sleep*, 2002b, 25: 224-231.
- Verster, J. C., Veldhuijzen, D. S., & Volkerts, E. R. Is it safe to drive a car when treated with anxiolytics? Evidence from on-the-road driving studies during normal traffic. *Curr Psychiat Rev*, 2005, 1: 215-225.
- Volkerts, E. R. & O'Hanlon, J. F. Residual effects on real car driving performance: zopiclone versus flunitrazepam and nitrazepam (Dutch with English summary and legends). *JDR J Drugther Res*, 1988, 13: 111-114.
- Vuurman, E. F. P. M. & Giorgetti, R. Effects of low and moderate doses of alcohol on actual driving in young novice drivers compared to experienced drivers. *Internal report*. Maastricht University, Department of Neuropsychology & Psychopharmacology, 2009.

CHAPTER 3

Wolschrijn, H., De Gier, J. J. & De Smet, P. A. G. M. Drugs and driving: a new categorization system for drugs affecting psychomotor performance. Maastricht, Institute for drugs, safety and behaviour, University of Limburg, 1991.

CHAPTER 4

On-the-road driving performance and driving related skills in untreated insomnia patients and chronic users of hypnotics

Leufkens TRM, Ramaekers JG, de Weerd AW, Riedel WJ, Vermeeren A.

ABSTRACT

It has not yet been clarified to what extent actual driving performance is affected by insomnia. In addition, it remains to be determined whether chronic use of hypnotics has deteriorating effects on driving performance in patients suffering from insomnia. Therefore, the aim of the present study was to explore the effects of insomnia and chronic use of hypnotics on driving in a one hour standardized driving test in actual traffic.

A total of 22 elderly insomnia patients chronically using hypnotics, 20 elderly insomniacs infrequently or not using hypnotics and 21 healthy, age-matched controls performed a standardized highway driving test between 10 and 11 hours after bedtime. Before the driving test cognitive performance was assessed.

Results indicate that driving performance is not impaired in patients suffering from insomnia, irrespective of use of hypnotics. In addition, driving related psychomotor and cognitive performance appeared not to be affected in medicated and unmedicated insomnia patients.

Insomnia patients appear to be able to successfully perform a one hour driving task that requires prolonged attentional demands. Chronic use of hypnotic does not seem to change driving performance.

INTRODUCTION

Approximately one-third of the general adult population suffers from insomnia, reporting difficulties in initiating sleep or in maintaining sleep, and feelings of nonrestorative sleep (Ohayon, 2002, Morin et al., 2006). Although non-pharmacological strategies, such as cognitive behavioral therapy, are increasingly being implemented in the treatment of insomnia, pharmacotherapy is still the most frequently used treatment for insomnia (Morin et al., 2007). The primary choice of sleep-enhancing medication is sedative hypnotics, such as benzodiazepines and the newer benzodiazepine receptor agonists zopiclone, zolpidem and zaleplon (Verster et al., 2007).

Ideally, a hypnotic should improve sleep and be free from residual sedative effects after arising. It is known, however, that a number of hypnotics that are currently prescribed can produce next-day residual sedation, depending on type of hypnotic, dose, time after administration and frequency of dosing (Vermeeren, 2004). This may lead to the impairment of a wide range of cognitive abilities and can have serious consequences for daily activities, such as driving a car. In epidemiological studies, for example, it has been shown that use of hypnotics is related to an increased risk of becoming involved in traffic and occupational accidents (Ray et al., 1992, Hemmelgarn et al., 1997, Barbone et al., 1998, Neutel, 1998, Dubois et al., 2008). Experimental studies assessing actual driving performance after administration of hypnotics confirm these data by showing residual driving impairment in the morning after dosing (Vermeeren, 2004).

In order to select the safest alternative among the available hypnotics, patients and prescribing physicians should be informed about the possible impairing effects of hypnotics. To date, information of the residual effects on driving performance is mainly derived from experimental studies conducted with young, healthy, hypnotic naïve volunteers after a single night of treatment. Investigating the residual effects in this population leaves two important issues unanswered. First, it may be possible that the effects of hypnotics interact with insomnia in such a way that they are experienced differently between insomniacs and healthy, young volunteers. Secondly, the majority of insomniacs uses hypnotics chronically, which may induce tolerance to their residual effects. As a consequence, the impairing effects may be less pronounced in insomniacs than in healthy volunteers.

Untreated insomniacs report reduced performance in daily life routines, which may have serious detrimental consequences (Chambers and Keller, 1993, Varkevisser and Kerkhof, 2005). It can, therefore, be expected that daytime performance after hypnotic-induced sleep is improved in insomniacs. Healthy volunteers, on the other hand, cannot benefit from hypnotic treatment as their performance is already optimal. Impairment observed due to hypnotic sedation in healthy volunteers may therefore be an overestimation of the net

effects of hypnotics in patients. However, two recent reviews found that most experimental studies examining cognitive and psychomotor performance did not reveal impaired daytime functioning in untreated insomnia patients (Riedel and Lichstein, 2000, Fulda and Schulz, 2001). Only minor impairment was found in tasks measuring attention span and vigilance (Fulda and Schulz, 2001).

Whereas experimental studies fail to demonstrate impaired daytime functioning, it has been shown in a cross-sectional epidemiological study that difficulties in sleeping are associated with an increased risk in occupational fatal accidents (Akerstedt et al., 2002). More recently, in a study investigating the relationship between health-related complaints and crash involvement risk, it was found that sleep disturbances were associated with an elevated risk of becoming involved in car accidents (Sagberg, 2006). The differences in findings of experimental and epidemiological research may be related to the type of research. A limitation of epidemiological studies is a lack of control for other factors contributing to impaired daytime functioning. For example, insomnia is strongly associated with disorders such as depression and anxiety (Stewart et al., 2006). These disorders have been shown to affect daily functions, including driving (Kindermann and Brown, 1997, Kizilbash et al., 2002, Wingen et al., 2006). The absence of objective impairment in experimental studies could be due to lack of laboratory tests demanding high effort (Vignola et al., 2000). Most performance tasks were of short duration and it has been suggested that insomniacs may relatively easily be able to maintain high level performance during testing (Varkevisser and Kerkhof, 2005).

The second issue that has not yet been clarified in experimental designs using single doses in healthy young volunteers is whether residual effects of hypnotics are still present in insomniacs who chronically use hypnotics. Although it is recommended not to use hypnotics for periods longer than four weeks, a majority of insomnia patients are treated for prolonged periods (Ashton, 2005, Paterniti et al., 2002). This may induce the development of tolerance to the residual effects of hypnotics (Bateson, 2002). For example, a recent experimental study demonstrated that performance of chronic users of

hypnotics was comparable to that of untreated insomnia patients and self defined good sleepers (Vignola et al., 2000).

In summary, it remains unclear whether insomnia has significant impairing consequences on daily life routines, such as driving a car. In addition, it has not been clarified if the use of hypnotics attenuates the presumed impairing effects of insomnia on driving performance. Furthermore, it remains to be investigated whether the residual effects on driving performance are absent in insomniacs chronically using hypnotics. Therefore, the primary objective of the present study was to compare actual driving performance between insomnia patients who chronically use hypnotics, insomnia patients who infrequently or do not use hypnotics and good sleepers. A second objective was to compare performance in driving related cognitive and psychomotor tasks between the three groups.

METHODS

Subjects

A total of 42 insomnia patients and 21 healthy controls, in the age range of 52 to 73 years, were recruited through a network of local general practitioners in the region of Maastricht, The Netherlands (Regionaal Netwerk Huisartsen, RNH) (Höppener et al., 1990, Metsemakers et al., 1992) and by advertisement in local newspapers. Insomnia patients had to meet the inclusion criteria for primary insomnia according to DSM-IV (APA, 1994): (i) subjective complaints of insomnia, defined as difficulties initiating sleep (sleep latency >30 min) and/or maintaining sleep (awakenings >30 min); (ii) duration of more than 1 month; (iii) the sleep disturbance causes clinically significant distress or impairment; (iv) insomnia does not occur exclusively during the course of a mental disorder and (v) insomnia is not due to another medical or sleep disorder or effects of medication or drug abuse. Healthy controls were self-defined good sleepers.

Sleep complaints of patients and healthy controls were measured using Dutch versions of the Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989), the Sleep Wake Experience List (SWEL) (van Diest et al., 1989) and the general version of the Groningen Subjective Quality of Sleep questionnaire

(GSQS-gen) (Mulder-Hajonides van der Meulen, 1981). Additionally, a daily journal and the specific version of the Groningen Subjective Quality of Sleep questionnaire (GSQS-spec) (Mulder-Hajonides van der Meulen, 1981) were completed upon arising each morning for two weeks providing subjective estimates of sleep quality.

Insomnia patients were assigned to one of two groups depending on the frequency and duration of their use of hypnotic drugs (benzodiazepine, zopiclone or zolpidem). Patients were assigned to a 'frequent users' group when they used a hypnotic for at least four nights per week and longer than three months (n=22). Patients not using hypnotics or using hypnotics less than or equal to three days per week were assigned to the 'infrequent users' group (n=20).

The hypnotics used in the frequent users group were zopiclone (n=4), temazepam (n=4), midazolam (n=4), oxazepam (n=3), zolpidem (n=2), lormetazepam (n=2), clonazepam (n=1), flurazepam (n=1) and nitrazepam (n=1). Average (\pm SD) duration of hypnotic use was 7.7 (6.8) years and average (\pm SD) frequency of use was 6.4 (1.2) nights a week (table 1).

In the 'infrequent users' group, 7 patients reported no history of hypnotic use. The remaining 13 patients used hypnotics infrequently and irregularly. Their average (\pm SD) nightly use was 4.1 (2.9) nights a month and with an average (\pm SD) duration of hypnotic use of 7.8 (7.9) years. The hypnotics used were temazepam (n=6), zopiclone (n=4), lorazepam (n=1), loprazolam (n=1) and nitrazepam (n=1).

All participants had to meet the following inclusion criteria: possession of a valid driving license for at least three years; average driving experience of at least 3000 km per year over the last three years; mentally and physically fit to drive; good health based on a pre-study physical examination, medical history, vital signs, electrocardiogram, blood biochemistry, haematology, serology and urinalysis; body mass index (BMI) between 19 and 30 kg/m².

Exclusion criteria were history of drug or alcohol abuse; presence of a significant medical, neurological, psychiatric disorder, or sleep disorder other than insomnia; chronic use of medication that affects driving performance,

except hypnotics; drinking more than 6 cups of coffee per day; drinking more than 21 alcohol containing beverages per week; smoking more than 10 cigarettes per day.

Participants were screened for major psychopathology by use of the Symptom Checklist 90 Revised (SCL-90-R) (Derogatis, 1983), the Beck Depression Inventory (BDI) (Beck et al., 1961), the State-Trait Anxiety Inventory (STAI) (Spielberger et al., 1983) and the Multidimensional Fatigue Inventory (MFI) (Smets et al., 1995).

During participation use of caffeine was prohibited from 8 hours prior to arrival on test days, until discharge the next morning. Alcohol intake was not allowed from 24 hours prior to each dosing until discharge. Smoking was prohibited from 1 hour prior to bedtime until discharge.

The study was conducted in accordance with the code of ethics on human experimentation established by the World Medical Association's Declaration of Helsinki (1964) and amended in Edinburgh (2000). The protocol was approved by the medical ethics committee of Maastricht University and University Hospital of Maastricht. Subjects were explained the aims, methods, and potential hazards of the study and they signed a written informed consent prior to any study-related assessments.

CHAPTER 4

Table 1. Overview of individual hypnotic use and their pharmacokinetic properties. Hypnotics are listed in increasing order of expected residual effects

Hypnotic	Dose (mg)	t _{1/2} (hours) ^a	Residual effects 8-12 hrs post dose ^c	Duration of use (years)	Nights per week	Gender	Age
zolpidem	10	1.9 ± 0.2	I (unlikely)	3	4	female	58
zolpidem	10	1.9 ± 0.2	I (unlikely)	10	7	male	59
midazolam	7.5	1.9 ± 0.6	I (unlikely)	1.5	7	male	68
midazolam	7.5	1.9 ± 0.6	I (unlikely)	5	7	male	64
midazolam	7.5	1.9 ± 0.6	I (unlikely)	4	7	male	64
midazolam	7.5	1.9 ± 0.6	I (unlikely)	3	7	female	57
lormetazepam	0.5	10 ± 2.5	I (unlikely)	7	6	male	55
temazepam	10	11	I (unlikely)	30	4	female	63
temazepam	10	11	I (unlikely)	4	4	male	65
temazepam	10	11	I (unlikely)	15	7	female	69
temazepam	20	11	I (unlikely)	1.5	7	female	56
zopiclone	3.75	5	I (unlikely)	3	7	female	58
zopiclone	3.75	5	I (unlikely)	15	7	female	63
zopiclone	3.75	5	I (unlikely)	2	7	female	60
nitrazepam	5	26 ± 3	II (minor)	12	7	female	68
zopiclone	7.5	5	II (moderate)	13	7	male	61
oxazepam	10	8 ± 2.4	NA	1.5	7	male	68
oxazepam	20	8 ± 2.4	NA	9	7	male	62
oxazepam	50	8 ± 2.4	II (moderate)	1	7	male	63
lormetazepam	2	10 ± 2.5	II (moderate)	10	4	male	63
flurazepam	15	1-2 (74 ± 24) ^b	II (moderate)	11	7	female	56
clonazepam	0.5	19-60	NA	7	7	female	67

^a Information derived from Vermeeren (2004), information about clonazepam derived from Riss et al. (2008); ^b half-life of active metabolite between brackets; ^c Hypnotics' residual effects are categorized according to a calibration scheme in which the impairment of a hypnotic is compared with blood alcohol concentrations (BAC). Category I = unlikely to produce an effect, equivalent to BAC <0.2 g/L; category II = likely to produce minor or moderate effects, equivalent to BAC 0.2-0.5 g/L; category III = likely to produce severe effects, equivalent to BAC >0.5 g/L (Wolschrijn et al., 1991, De Gier et al., 2009); NA = information not available

Assessments*Sleep*

On nights before testing sleep quality and duration was measured by polysomnography using montage including electroencephalogram (EEG), electrooculogram (EOG) and electromyogram (EMG). Sleep stages were visually assessed by experienced technicians according to standardized criteria (Iber et al., 2007). Parameters derived after analysis are sleep onset latency (SOL, in min); wake after sleep onset (WASO, in min); total sleep time (TST, in min); sleep efficiency (SE, in %); and number of awakenings (NA).

Upon arising subjects completed the specific version of the Groningen Subjective Quality of Sleep questionnaire (GSQS-spec) (Mulder-Hajonides van der Meulen, 1981), providing a score representing number of sleep complaints; and subjective estimations of sleep onset latency (in min), number of awakenings and total sleep time (in min).

Driving performance

Driving performance was assessed using two standardized driving tests developed to measure different aspects of driving performance. The primary test is the Highway Driving Test (O'Hanlon, 1984) which measures road tracking performance. Performance in this test is mainly determined by the delay lag between sensory information, execution of motor reaction and the vehicle's dynamic response. In this test, subjects operate a specially instrumented vehicle over a 100 km (61 mi) primary highway circuit, accompanied by a licensed driving instructor having access to dual controls. The subjects' task is to maintain a constant speed of 95 km/h (58 mi/h) and a steady lateral position between the delineated boundaries of the slower traffic lane. The vehicle speed and lateral position are continuously recorded. These signals are edited off line to remove data recorded during overtaking maneuvers or disturbances caused by roadway or traffic situations. The remaining data are then used to calculate means and standard deviations of lateral position and speed. Standard deviation of lateral position (SDLP in centimeters) is the primary outcome

variable. SDLP is a measure of road tracking error or 'weaving'. The test duration is approximately 1 hour.

The Car-Following Test (Brookhuis et al., 1994, Ramaekers and O'Hanlon, 1994) measures changes in controlled information processing such as selective attention, stimulus interpretation and decision making, and speed of an adaptive motor response to events which are common in driving. In the test two vehicles travel in tandem over a 2-lane, undivided, secondary highway at 70 km/h (44 mi/h). An investigator drives the leading car and the subject, in the second car, is instructed to follow at a distance between 25 and 35 meter. Subjects are further instructed to constantly attend the leading car since it may slow down or speed up at unpredictable times. They are required to follow the leading car's speed movements, i.e. maintain the initial headway by matching the velocity of the car to the other's. During the test, the speed of the leading car is automatically controlled by a modified 'cruise control' system. At the beginning it is set to maintain a constant speed of 70 km/h and, by activating a microprocessor the investigator can start sinusoidal speed changes reaching amplitude of -10 km/h and returning to the starting level within 50 sec. The maneuver is repeated 6 times. The leading car's speed and signals indicating the beginning of the maneuver are transmitted via telemetry to be recorded in the following vehicle together with the following vehicle's speed. Phase-delay converted to a measure of the subject's average reaction time to the movement of the leading vehicle (RT, in s) is taken as the primary dependent variable in this test. Headway is continuously recorded by means of an optical distance sensor and serves as a control variable. Test duration is 25 minutes.

Cognitive and psychomotor performance

Cognitive and psychomotor performance was assessed by tests for word learning, digit span, tracking, divided attention, sustained attention and inhibitory control. Tests were selected based on their sensitivity to residual sedating effects of hypnotics or sleep disturbances, and their relation to driving performance (Vermeeren et al., 1995, Vermeeren et al., 1998, Fulda and

Schulz, 2001, Vermeeren et al., 2002, Verster et al., 2002, Vermeeren, 2004, Leufkens et al., in press, Leufkens and Vermeeren, in press).

The Word Learning Test (Rey, 1964) is a verbal memory test for the assessment of immediate recall, delayed recall and recognition performance. Fifteen monosyllabic nouns are presented and at the end of the sequence the subject is asked to recall as many words as possible. This procedure is repeated five times and after a delay of at least 30 minutes the subject is again required to recall as many words as possible. At this trial the nouns are not presented. Finally, a sequence of 30 monosyllabic nouns is presented, containing 15 nouns from the original set and 15 new nouns in random order. The subject has to indicate whether a noun originates from the old set or it is from a new set of nouns.

The Digit Span Forward and Backward is a subtest of the Wechsler Adult Intelligence Scale-Revised (WAIS-R) (Wechsler, 1981). In this test, subjects are asked to repeat orally presented digits with increasing sequence length, either in forward or reverse order. There are two trials at each series length, and the test continues until both trials of a series length are failed. One point is awarded for each correct trial.

The Critical Tracking Test (Jex et al., 1966) measures the ability to control an unstable signal in a tracking task. The signal deviates horizontally from a midpoint and the subject has to compensate this signal deviation by moving a joystick in opposite direction. The test includes five trials of which the lowest and the highest score are discarded.

The Divided Attention Task (Moskowitz, 1973) measures the ability to divide attention between two simultaneously performed tasks. The first task is to perform the CTT at a constant level of difficulty set at 50% of his or her maximum capacity. In the other task the subject has to monitor 24 single digits that are presented in the four corners of the screen. The digits change asynchronously at 5-second intervals. The subjects are instructed to remove their foot from a pedal as rapidly as possible whenever the digit '2' appears. This signal occurs twice at every location, in random order, at intervals of 5 to 25 sec.

CHAPTER 4

In the Stop Signal Task (Logan et al., 1984) the concept of inhibitory control is defined as the ability to stop a pending thought or action and to begin another. The paradigm consists of two concurrent tasks, i.e. a go task (primary task) and a stop task (secondary task). The go signals (primary task stimuli) are two letters ('X' or 'O') presented one at a time in the center of a computer screen. Subjects are required to respond to each letter as quickly as possible by pressing one of two response buttons. Occasionally, a stop signal (secondary task stimulus) occurs during the test. The stop signal consists of an auditory cue, i.e. a 1000 Hz tone, that is presented for 100 ms. The interval at which the stop signal is presented is dependent from the subject's own successful and unsuccessful inhibitions. By continuously monitoring the subject's response the stop signal reaction time is calculated during the task. Subjects are required to withhold any response in case a stop signal is presented.

The Psychomotor Vigilance Task (Dinges and Powell, 1985) is based on a simple visual RT test. Subjects are required to respond to a visual stimulus presented at variable interval (2000 to 10000 msec) by pressing either the right or the left button with the dominant hand. The visual stimulus is a counter turning on and incrementing from 0 to 60 sec at 1-msec intervals. In response to the subject's button press, the counter display stops incrementing, allowing the subject 1 sec to read the RT before the counter restarts. If a response has not been made in 60 sec, the clock resets and the counter restarts.

Subjective evaluations

Subjective evaluations of mood, sedation and driving quality were assessed using a series of visual analogue scales (100 mm). The subjects were instructed to rate their subjective feelings using a 16-item mood scale which provides three factor analytically defined summary scores for 'alertness', 'contentedness', and 'calmness' (Bond and Lader, 1974).

Subjective feelings of sleepiness were rated with the Karolinska Sleepiness Scale (Akerstedt and Gillberg, 1990), ranging from 1 (extremely alert) to 9 (very sleep, fighting sleep).

Subjects rated the degree of mental effort to perform the driving performance with the Rating Scale Mental Effort (Zijlstra, 1993). The scale is a visual analogue scale (150 mm) with additional verbal labels.

The driving instructors rated each subject's driving quality and apparent sedation at the conclusion of the Highway Driving Test, using two 100 mm visual analogue scales.

Procedure

Subjects were individually trained to perform the laboratory tests during two sessions of approximately 1.5 hours within 10 days before their first night. After training the subjects underwent two nights of sleep evaluation. The first night was a habituation and practice condition to familiarize subjects with the sleeping facilities and polysomnographic and test procedures. The second night was considered as the actual test condition.

A test condition started in the evening of Day 1, when the subjects arrived at the site at approximately 19:00 hours, and lasted until Day 2, when they were discharged at approximately 11:45 hours. On arrival at the sleeping facility, subjects rated their subjective feelings and subjective sleepiness. From 19:30 hrs until 20:30 hrs they performed the first session of laboratory tests, comprising the Word Learning Test immediate and first delayed recall, the Critical Tracking Task, the Divided Attention Task, the Psychomotor Vigilance Task, the Stop Signal Task, and the Digit Span forward and backward. Hereafter, electrodes for polysomnographic recording were attached.

Subjects retired to bed at 23:30 hrs. Immediately preceding retiring, subjects in the 'medicated insomnia' group ingested their own prescribed hypnotic, whereas subjects in the 'unmedicated insomnia' group and controls did not ingest medication. Subjects were awakened at 07:30 hrs and after arising a light standardized breakfast was served. At 08:00 hrs subjects evaluated sleep quality and duration, and feelings of daytime sleepiness and alertness. Subsequently, they started the second session of laboratory tests, comprising the Word Learning Test second delayed recall and recognition, the Critical Tracking Task, the Divided Attention Task, the Psychomotor Vigilance Task,

CHAPTER 4

and the Digit Span forward and backward. At 9:00 hrs subjects were transported to the Highway Driving Test which they performed between 09:30 and 10:30 hrs. Upon completion subjects rated the mental effort it took to perform this driving test, and subsequently they conducted the Car-Following Test. Upon completion of this test subjects returned to the testing facilities for removal of the electrodes and were discharged.

Statistical analysis

The primary parameter of the study was the Standard Deviation of Lateral Position (SDLP, in cm). Driving and sleep related parameters were compared between the three groups, using a one-way analysis of variance with *Group* as between subject factor with three levels ('frequent users', 'infrequent users', 'controls'). Parameters which were assessed in evening and morning session were analyzed using 2x3 Repeated Measures analysis with *Session* as within subject factor with two levels (evening, morning) and *Group* as between subject factor. Significant ($p < 0.05$) main effects or interactions, were further analyzed using three univariate comparisons between groups for each session separately and paired t-tests between sessions for each group separately. If the model assumptions were violated, a suitable transformation or nonparametric method was chosen for analysis.

All statistical analyses were done by using the Statistical Package for the Social Sciences (SPSS) statistical program (version 15.0 for Windows; SPSS, Chicago, IL).

RESULTS

Pre-study group characteristics

Table 2 illustrates the descriptive variables of sociodemographic, sleep and psychological data. One-way ANOVA showed that there were no differences between the groups in years of age, years of education, average annual mileage and years of possession of a driving license.

There were overall significant differences on a large number of parameters of sleep evaluation at home. Both insomnia groups scored significantly higher on the PSQI than the control group (both $p < 0.001$). There were no differences between the insomnia groups in PSQI score. The insomnia groups reported significantly more sleep complaints on the GSQS than the control group (both $p < 0.001$), but did not differ in complaints from each other. Evaluation of the SWEL revealed that approximately 50% of both insomnia groups reported having sleep initiation and sleep maintenance problems, and early morning awakenings, whereas none of the controls reported having these difficulties.

Analysis of the SCL-90R showed that there was a significant overall group difference on the anxiety, depression, somatization, cognitive insufficiency, sleeping problems and psychoneuroticism subscales. With the exception of the anxiety subscale, in all other subscales both insomnia groups differed significantly from the control group (depression: both $p = 0.004$; somatization: frequent users $p = 0.002$ and infrequent users $p = 0.027$; cognitive insufficiency: frequent users $p = 0.021$ and infrequent users $p = 0.041$; sleeping problems: both $p < 0.001$; psychoneuroticism: frequent users $p = 0.001$ and infrequent users $p = 0.003$). There were no differences between the insomnia groups on any of the subscales.

Overall significant differences were found on the BDI and on the two subscales of the STAI. Post-hoc analysis showed that the insomnia groups scored higher on all scales when compared to the control group (BDI: both $p = 0.001$; STAI state: frequent users $p = 0.044$ and infrequent users $p < 0.001$; STAI trait: frequent users $p = 0.005$ and infrequent users $p < 0.001$). The insomnia groups did not score differently from each other on BDI and STAI.

Statistical analysis of the MFI revealed overall significant differences on all five subscales. Post-hoc comparisons showed that both insomnia groups reported suffering from significantly more general fatigue (both $p < 0.001$), significantly more physical fatigue (both $p < 0.001$) and more mental fatigue (frequent users $p < 0.001$ and infrequent users $p = 0.002$) when compared to the control group. In addition, both groups had significantly higher scores on the reduced motivation scale compared to the control group (frequent users

CHAPTER 4

$p=0.015$ and infrequent users $p=0.027$). Scores on the reduced activity scale were only significantly higher in the frequent users group as compared to the controls ($p=0.040$). No differences between the insomnia groups were found on any of the scales.

INSOMNIA PATIENTS AND DRIVING PERFORMANCE

Table 2. Means (\pm SD) of pre-study group characteristics

Variable	Frequent users (n = 22)	Infrequent users (n = 20)	Controls (n = 21)	F
<i>Sociodemographics</i>				
Age (years)	62.1 (4.4)	60.8 (5.9)	61.7 (5.0)	.40
Education (years)	12.3 (3.3)	10.9 (2.7)	13.2 (3.3)	2.67
Average Annual Mileage (km)	8525 (6269)	11875 (11534)	9655 (4157)	.98
Driving License (years)	38.0 (8.3)	39.0 (8.4)	40.6 (5.9)	.64
<i>Sleep</i>				
Pittsburgh Sleep Quality Index	12.6 (3.5) ^a	12.6 (2.6) ^a	2.4 (1.6)	100.20 ^{***}
Groningen Subjective Quality of Sleep - general	9.4 (3.0) ^a	11.1 (1.7) ^{a,b}	1.0 (1.5)	126.08 ^{***}
Sleep Wake Experience List [†]				
Sleep Initiation Problems	12 ^a	10 ^a	0	16.73 ^{***}
Sleep Maintenance Problems	14 ^a	13 ^a	0	23.26 ^{***}
Early Morning Awakenings	15 ^a	5 ^a	0	7.61 [*]
Difficulty Waking Up	2	2	0	2.12
Tiredness Upon Waking Up	3	2	0	2.86
Daytime Sleepiness	5	3	1	2.80
<i>Psychological</i>				
Symptom Checklist 90-R				
Anxiety	15.8 (7.3) ^a	13.9 (4.8)	10.8 (1.3)	5.28 ^{**}
Phobic anxiety	8.9 (4.5)	7.4 (1.0)	7.3 (0.8)	2.42
Depression	26.7 (9.7) ^a	27.1 (10.7) ^a	18.0 (3.0)	7.62 ^{***}
Somatization	20.5 (7.9) ^a	19.1 (5.9) ^a	14.2 (1.8)	6.80 ^{**}
Cognitive Insufficiency	16.1 (6.3) ^a	15.8 (8.1) ^a	11.0 (1.8)	4.78 [*]
Interpersonal Sensitivity	25.8 (6.5)	24.8 (8.4)	21.7 (5.6)	2.11
Hostility	7.4 (1.6)	7.9 (2.8)	6.8 (1.3)	1.41
Sleeping Problems	9.6 (3.1) ^a	10.0 (2.5) ^a	3.3 (0.7)	52.57 ^{***}
Psychoneuroticism	141.9 (37.1) ^a	137.9 (39.6) ^a	103.0 (13.1)	9.37 ^{***}
Beck Depression Inventory	8.6 (5.0) ^a	8.6 (6.6) ^a	2.8 (3.0)	9.38 ^{***}
State Trait Anxiety Inventory				
State Anxiety	35.3 (10.1) ^a	41.6 (11.0) ^a	28.1 (7.5)	10.03 ^{***}
Trait Anxiety	38.4 (10.9) ^a	41.9 (13.1) ^a	27.6 (5.8)	9.30 ^{***}

Table 2. continued from p. 113

Variable	Frequent users (n = 22)	Infrequent users (n = 20)	Controls (n = 21)	F
Multidimensional Inventory				
General Fatigue	11.8 (3.7) ^a	11.9 (3.7) ^a	6.8 (2.5)	16.36 ^{***}
Physical Fatigue	10.9 (3.5) ^a	10.6 (3.5) ^a	6.6 (2.3)	12.23 ^{***}
Reduced Activity	10.1 (4.2) ^a	10.0 (3.2)	7.4 (2.6)	4.03 [*]
Reduced Motivation	9.8 (3.6) ^a	9.6 (4.2) ^a	6.7 (2.5)	5.29 ^{**}
Mental Fatigue	11.5 (3.9) ^a	10.8 (3.5) ^a	7.0 (2.4)	11.24 ^{***}

^{*} = values for each variable are the frequencies in each group. Statistical analysis was conducted with the Kruskal-Wallis test, depicted are the Chi-square values; ^{*} = p<0.05; ^{**} = p<0.01; ^{***} = p<0.001; ^a = significant difference with control group (p<0.05; post-hoc analysis with Bonferroni correction); ^b = significant difference between frequent and infrequent users (p<0.05; post-hoc analysis with Bonferroni correction)

Pre-study sleep diary

Statistical analysis of the sleep diary showed overall significant differences on all parameters, except the time spent in bed (table 3). Compared with the healthy, good sleepers, the infrequent users group reported significantly more sleep complaints (p<0.001), a significantly longer sleep onset time (p<0.018), shorter total sleep time (p<0.001), worsened sleep efficiency (p<0.001), earlier morning awakenings (p<0.018) and more awakenings (p<0.001). Sleep quality in the frequent users group was significantly worse as compared to the good sleepers in number of sleep complaints (p<0.001), sleep onset time (p<0.018) and sleep efficiency (p<0.017). Comparisons between the two insomnia groups revealed that the frequent users reported a longer total sleep time (p<0.008), better sleep efficiency (p<0.016) and less awakenings (p<0.023) than the infrequent users.

Table 3. Sleep diary

Variable	Frequent users (n = 22)	Infrequent users (n = 20)	Controls (n = 21)	F	p
<i>Groningen Subjective Quality of Sleep scale</i>	6.0 (2.6) ^a	6.8 (2.0) ^a	1.9 (1.1)	32.76	<.001
<i>Sleep Onset Time (min)</i>	43.0 (36.9) ^a	43.6 (29.8) ^a	18.3 (4.1)	5.44	.007
<i>Total Sleep Time (min)</i>	410.9 (73.1) ^b	348.5 (71.2) ^a	440.3 (36.8)	10.63	<.001
<i>Time in Bed (min)</i>	521.0 (61.1)	498.9 (52.7)	495.1 (36.8)	1.53	.226
<i>Sleep Efficiency (%)</i>	79.3 (13.3) ^{a,b}	69.2 (11.8) ^a	89.2 (6.7)	16.09	<.001
<i>Early Morning Awakening (min)</i>	33.1 (42.6)	50.0 (41.5) ^a	17.8 (13.8)	4.07	.022
<i>Number of Awakenings</i>	0.75 (0.69) ^b	1.38 (0.93) ^a	0.46 (0.44)	8.50	.001

^a = significant difference with control group ($p < 0.05$; post-hoc analysis with Bonferroni correction);

^b = significant difference between frequent and infrequent users ($p < 0.05$; post-hoc analysis with Bonferroni correction)

Objective and subjective sleep evaluation

Table 4 presents the sleep parameters of the objective and subjective sleep evaluation for each group. Results were derived from the second night at the sleeping facilities. There were no differences between the three groups on any of the objective sleep parameters. In contrast, a significant overall group difference was found on subjective evaluation of sleep complaints ($F_{2,63}=6.24$, $p < 0.003$). Post-hoc comparisons showed that both insomnia groups reported significantly more sleep complaints on the GSQS than the control group (frequent users: $p < 0.043$; infrequent users: $p < 0.004$).

In addition, subjective reports on early morning awakenings appeared to differ significantly between the groups as well ($F_{2,63}=3.23$, $p < 0.046$). The infrequent users group reported to be awake significantly earlier than the control group ($p < 0.042$). The frequent users group did not differ from the control group with respect to early morning awakenings.

There were no significant group differences on the subjective sleep measures of sleep onset time, number of awakenings and total sleep time.

Table 4. Mean (\pm SD) of objective and subjective sleep parameters

Variable	Frequent users (n = 22)	Infrequent users (n = 20)	Controls (n = 21)	F	p
<i>Sleep Onset Time (minutes)</i>					
Polysomnography	26.4 (9.4)	19.4 (13.4)	19.2 (14.6)	2.20	.120
Subjective Evaluation	47.6 (97.9)	67.9 (73.0)	33.0 (36.8)	1.19	.321
<i>Total Sleep Time (minutes)</i>					
Polysomnography	383 (35)	389 (46)	408 (40)	2.15	.125
Subjective Evaluation	351 (101)	302 (94)	377 (111)	2.92	.062
<i>Number of Awakenings</i>					
Polysomnography	7.9 (4.1)	10.2 (4.3)	7.5 (4.5)	2.37	.102
Subjective Evaluation	2.1 (1.6)	3.0 (2.5)	1.8 (1.5)	1.97	.149
<i>Polysomnographic parameters</i>					
Sleep Efficiency (%)	79.6 (8.8)	80.8 (9.5)	84.6 (8.1)	1.82	.170
Wake After Sleep Onset (minutes)	76.5 (65.0)	73.1 (39.4)	55.2 (35.7)	1.16	.321
Stage 1 Sleep (% of Total Sleep Time)	6.6 (2.9)	6.9 (2.4)	6.1 (3.0)	0.50	.612
Stage 2 Sleep (% of Total Sleep Time)	56.6 (6.1)	54.5 (6.5)	56.0 (9.0)	0.44	.644
Stage SWS Sleep (% of Total Sleep Time)	18.4 (8.5)	18.5 (5.9)	16.5 (5.5)	0.58	.566
Stage REM Sleep (% of Total Sleep Time)	18.4 (4.3)	20.1 (5.8)	21.4 (6.0)	1.61	.209
<i>Subjective Evaluation</i>					
Early Morning Awakening (minutes)	49.1 (57.5)	67.4 (62.0) ^a	26.4 (34.7)	3.23	.046
Groningen Subjective Quality of Sleep scale	6.7 (3.9) ^a	7.8 (3.8) ^a	3.9 (3.5)	6.24	.003

^a = significant difference with control group ($p < 0.05$; post-hoc analysis with Bonferroni correction);

^b = significant difference between frequent and infrequent users ($p < 0.05$; post-hoc analysis with Bonferroni correction)

Driving, cognitive and psychomotor performance

Statistical analysis of the driving tests and the cognitive and psychomotor tests revealed no significant differences between the three groups on any of the performance tests (table 5 and 6). Comparisons between evening and morning sessions showed that there was a significant difference between evening and

morning average reaction time of the PVT ($F_{1,59}=8.57$, $p<0.005$). The control group appeared to have a significant lower reaction time in the morning as compared to the evening session ($p<0.005$).

Subjective rating scales

Analysis of the subjective evaluation of mood revealed an overall significant group difference in feelings of alertness ($F_{2,60}=4.44$, $p<0.016$). Post-hoc comparisons showed that the frequent users group felt significantly less alert in the morning than the control group ($p<0.013$). In addition, the control group felt more alert in the evening when compared to the morning ($p<0.004$).

Scores on the Karolinska Sleepiness Scale were not different between the three groups. There was, however, a significant between the evening and morning evaluation ($F_{1,60}=7.25$, $p<0.009$). The control group reported significantly more feelings of sleepiness in the morning as compared to the evening ($p<0.006$).

Table 5. Mean (\pm SD) of driving performance parameters

Variable	Frequent users (n = 22)	Infrequent users (n = 20)	Controls (n = 21)	F	p
<i>Highway Driving Test</i>					
Standard Deviation of Lateral Position (in cm)	17.4 (4.3)	17.7 (2.9)	16.8 (2.7)	0.38	.688
Mean Speed (in km/h)	94.5 (1.5)	93.9 (1.9)	94.3 (1.4)	0.94	.396
Standard Deviation of Speed (in km/h)	2.11 (0.5)	2.34 (0.7)	2.18 (0.7)	0.76	.471
<i>Car Following Test</i>					
Reaction time (in sec)	3.55 (1.57)	3.32 (1.40)	3.06 (1.01)	0.67	.518
Headway	1.14 (0.13)	1.21 (0.25)	1.15 (0.12)	0.94	.397
<i>Subjective Evaluation of Driving Test</i>					
Subjective Driving Quality	67.0 (11.2)	67.9 (9.7)	65.0 (13.9)	0.34	.713
Apparent Sedation	11.9 (11.4)	12.2 (14.9)	9.1 (10.2)	0.42	.657
Mental Effort	30.3 (22.6)	35.7 (24.9)	20.3 (14.1)	2.77	.071

CHAPTER 4

Table 6. Mean (\pm SD) of psychomotor and cognitive performance parameters

Variable	Frequent users (n = 22)	Infrequent users (n = 20)	Controls (n = 21)	F ^a	p
<i>Critical Tracking Task</i>					
Average lambda (in rad/sec) <i>evening</i>	3.34 (0.72)	3.23 (0.60)	3.03 (0.49)	0.06	.945
Average lambda (in rad/sec) <i>morning</i>	3.29 (0.70)	3.21 (0.72)	3.02 (0.49)		
<i>Divided Attention Task</i>					
Tracking subtask: Average Error (in mm) <i>evening</i>	14.1 (5.2)	14.4 (4.4)	17.4 (5.2)	0.75	.478
Tracking subtask: Average Error (in mm) <i>morning</i>	15.5 (5.9) ^b	14.9 (4.2)	18.7 (5.2)		
Detection subtask: Reaction Time (in msec) <i>evening</i>	1924 (328)	1974 (299)	1973 (335)	2.56	.086
Detection subtask: Reaction Time (in msec) <i>morning</i>	2030 (344)	1898 (288)	1920 (338)		
<i>Stop Signal Task</i>					
Go Reaction Time (in msec)	423 (63)	427 (77)	422 (50)	0.03	.972
Stop Signal Reaction Time (in msec)	179 (35)	178 (31)	181 (35)	0.05	.953
<i>Psychomotor Vigilance Task</i>					
Average Reaction Time (in msec) <i>evening</i>	269 (39)	257 (32)	264 (24)	1.33	.273
Average Reaction Time (in msec) <i>morning</i>	264 (39)	254 (34)	251 (22) ^b		
Median Reaction Time (in msec) <i>evening</i>	254 (34)	244 (31)	247 (23)	0.50	.610
Median Reaction Time (in msec) <i>morning</i>	252 (35)	242 (30)	241 (21)		
Lapses (>500 msec) <i>evening</i>	1.2 (2.0)	1.3 (1.1)	1.0 (1.3)	0.73	.486
Lapses (>500 msec) <i>morning</i>	1.3 (2.1)	0.7 (1.0)	0.7 (1.2)		
<i>Word Learning Task</i>					
Immediate Total Recall Score	46.3 (12.3)	46.8 (9.4)	49.4 (9.0)	0.53	.590
Delayed Recall Score <i>evening</i>	7.8 (3.5)	8.4 (2.9)	8.9 (3.4)	0.14	.870
Delayed Recall Score <i>morning</i>	6.5 (2.5) ^b	7.0 (3.4) ^b	7.3 (3.2) ^b		
Recognition Score	24.8 (4.4)	24.6 (3.0)	25.7 (3.4)	0.49	.615
Recognition Reaction Time (in msec)	924 (189)	892 (192)	883 (141)	0.33	.722

Table 6. continued from p. 118

Variable	Frequent users (n = 22)	Infrequent users (n = 20)	Controls (n = 21)	F ^a	p
<i>Digit Span</i>					
Forward Score <i>evening</i>	3.6 (1.3)	3.8 (1.1)	3.9 (1.2)	1.43	.248
Forward Score <i>morning</i>	3.5 (0.9)	4.0 (1.1)	4.4 (1.1)		
Backward Score <i>evening</i>	3.5 (1.3)	3.9 (1.4)	4.3 (1.1)	0.04 ^a	.965
Backward Score <i>morning</i>	3.3 (1.0) ^c	3.8 (1.4)	4.2 (1.1)		
<i>Subjective Evaluations of Feelings</i>					
Alertness <i>evening</i>	65.9 (16.7) ^c	73.8 (13.2)	81.4 (13.4)	1.05	.356
Alertness <i>morning</i>	64.3 (18.6)	69.4 (14.0)	74.4 (14.6) ^b		
Contentedness <i>evening</i>	72.5 (21.2)	78.3 (13.0)	82.7 (12.6)	0.56	.576
Contentedness <i>morning</i>	74.8 (19.0)	76.3 (12.1)	81.1 (13.6)		
Calmness <i>evening</i>	69.8 (22.5)	74.9 (14.0)	82.4 (13.9)	0.62	.542
Calmness <i>morning</i>	72.7 (17.3)	73.0 (13.9)	79.8 (14.4)		
Karolinska Sleepiness Scale <i>evening</i>	3.9 (1.7)	3.9 (1.7)	3.0 (0.8)	0.26	.770
Karolinska Sleepiness Scale <i>morning</i>	4.6 (1.5)	4.3 (1.7)	3.8 (1.3) ^b		

^a = test for *Session* by *Group* interaction, except for the Stop Signal Task which was only assessed in the evening session; ^b = significant *Session* effect $p < 0.05$; ^c = significant difference from control group $p < 0.05$

DISCUSSION

The present experimental study is the first directly comparing driving performance between insomnia patients who chronically use hypnotics, insomnia patients who do not or infrequently use hypnotics and healthy, good sleepers. Results show that driving, as measured by a standardized highway driving test and a car-following test, is not impaired in insomniacs, irrespective of the use of hypnotics. In addition, the present study shows that driving related psychomotor and cognitive performance is not different between insomnia patients and healthy, good sleepers.

Results of the study corroborate previous findings showing an absence of neuropsychological deficits in both pharmacologically treated and untreated insomniacs (Vignola et al., 2000). Aside from minor attentional problems in

insomniacs, as reflected by lower scores in the digit span forward test, the study by Vignola reported no significant differences in performance between treated insomniacs, untreated insomniacs and healthy, good sleepers. The authors suggested, however, that the absence of cognitive impairment may have been due to methodological limitations. The tests used in their study were of short duration and demanded low effort (e.g. digit symbol substitution test and purdue pegboard test). Consequently, insomnia patients may have been able to exert enough effort for a short period to complete the tests successfully.

In the present study, subjects performed a standardized highway driving test for approximately 1 hour. The prolonged attentional demands of the task were expected to reveal possible performance deficits in insomnia patients, which were not found with tasks of short duration. Yet, there were no indications of deterioration in driving performance in insomnia patients, irrespective of use of hypnotics. These results can be interpreted in two ways. First, sleep in the insomnia groups was undisturbed according to polysomnographic criteria leaving daytime performance unaffected. Despite significantly more subjective sleep complaints reported by the insomniacs when compared with the healthy, good sleepers, there was no objective evidence for any sleeping problems. Discrepancies between subjective and objective sleep parameters are characteristic in a majority of insomnia patients (e.g. Carskadon et al., 1976, Orff et al., 2007, Vignola et al., 2000). It is suggested, therefore, that the current standards of sleep analysis may not be adequate for distinguishing insomnia from healthy, undisturbed sleep (Bastien et al., 2003). A possible solution can be found in spectral analysis of the sleep microstructure, dissociating characteristic electroencephalographic activities.

The lack of objectively measured sleep complaints may be also due to the sleeping environment. Home-based polysomnographic recordings have shown that insomnia patients' sleep appears more disturbed when they sleep at home than when they sleep at the laboratory (Edinger et al., 1997). Indeed, in the present study, subjective sleep evaluations showed that sleep quality in the laboratory improved in both insomnia groups compared to sleep at home. In addition, subjective sleep quality for the healthy controls was worse during

laboratory sleep than at home. These changes in sleep quality may have diminished differences between the groups.

A second explanation for the absence of impairment in driving performance may be that the insomnia patients, who had ample driving experience, may have been easily able to complete the driving tests successfully. In a recent study it has been shown that establishing performance impairment in insomnia may be dependent on task complexity (Altena et al., 2008). Insomnia patients performed worse than healthy controls only in a complex vigilance task, whereas the patients' performance in a simple reaction time task appeared to be even better than healthy controls. The authors concluded that chronic insomnia is associated with cognitive dysregulation, but that this may only be revealed in tasks measuring higher-level functioning. Highway driving is a well practiced and highly automated skill (Brouwer, 2002) which may not require such high cognitive demands in experienced drivers. Judging from the low scores on the mental effort scale this assumption seems to be confirmed. Scores on the scale can range from 0 to 150. The average scores in the present study were 30.3 for the medicated insomnia patients, 35.7 for the unmedicated insomnia patients and 20.3 for the healthy controls (indicating low to little effort). In a study comparing cognitive performance between patients with seasonal allergic rhinitis and healthy controls, subjects evaluated the mental effort they had to put in a 45 minutes sustained attention test considerably higher (Hartgerink-Lutgens et al., in press). Mental effort scores were around 90 for both groups, indicating substantial higher demands of that test as compared with the highway driving test. Yet, the insomniacs, in particular the frequent users group, evaluated the degree of mental effort they had to put in the driving test tentatively higher than the healthy controls. Although not reaching statistical significance, this may suggest that the insomnia patients compensated possible performance difficulties by increasing their effort.

In addition to the findings that driving is not affected in insomnia patients, results of the present study show that driving is not impaired in patients chronically using hypnotics as well. The absence of impairment, combined with the still present subjective sleep complaints suggests the development of, at

least partial, tolerance to both therapeutic and residual effects of hypnotics. With respect to the residual effects, the results are partly supported by epidemiological data (Neutel, 1998), showing that prolonged use of hypnotics is associated with a lowered risk of becoming involved in a car accident when compared with initial use of hypnotics. Nevertheless, the risk of injurious traffic accidents after chronic use of hypnotics remained twice as high in long-term hypnotic users in comparison to healthy, unmedicated drivers.

The absence of residual effects in the present study may be explained by the wide variety of hypnotic drugs and doses used in the frequent users group, however. Most importantly, the majority of hypnotics and doses used were unlikely to produce residual effects. Consequently, the large differences in degree of residual effects may have contributed to the variability of performance in this group and masked any detectable impairment which is only associated with hypnotics belonging to category II or III, i.e. drugs and doses judged likely to produce moderate or severe impairment (Wolfschrijn et al., 1991, De Gier et al., 2009). This was confirmed by post hoc inspection of the average SDLP scores from the category I users and the category II users. The average (\pm SD) SDLP scores of the group who used hypnotics belonging to category I was 16.8 (4.7) cm, whereas it was 18.3 (3.5) cm in the group using category II hypnotics. Future research in patients chronically using the same hypnotic is needed to shed more light on this issue. The present study aimed, however, to evaluate driving performance in a representative, non-selective study sample of insomnia patients chronically using hypnotics.

It may be argued that the driving tests are not sensitive enough to detect performance deficits as a consequence of a disorder. Studies assessing driving performance in other patient groups using the same standardized driving test have been conducted previously with 14 patients with chronic nonmalignant pain (Veldhuijzen et al., 2006) and 24 depressed patients receiving long-term antidepressant treatment (Wingen et al., 2006). In contrast to the present study, these studies showed that driving was significantly impaired in both patient groups as compared with healthy controls. These results suggest that the driving test has sufficient sensitivity for detecting driving impairment in patient

groups. In addition, sample sizes of the previous studies were similar to the present study, suggesting that the absence of effects of insomnia could not be explained in terms of statistical power. Finally, it may be suggested that the effects of insomnia are less debilitating than the effects of pain and depression.

To conclude, results of the present study indicate that driving performance is not impaired in patients suffering from insomnia, irrespective of use of hypnotics. In addition, driving related psychomotor and cognitive performance appears not to be affected in medicated and unmedicated insomnia patients. Therefore, studies investigating residual effects of hypnotics on driving performance in healthy volunteers are not expected to yield different results than in insomnia patients.

REFERENCES

- Akerstedt, T., Fredlund, P., Gillberg, M. & Jansson, B. A prospective study of fatal occupational accidents -- relationship to sleeping difficulties and occupational factors. *J Sleep Res*, 2002, 11: 69-71.
- Akerstedt, T. & Gillberg, M. Subjective and objective sleepiness in the active individual. *Internat J Neurosc*, 1990, 52: 29-37.
- Altena, E., Van Der Werf, Y. D., Strijers, R. L. M. & Van Someren, E. J. W. Sleep loss affects vigilance: Effects of chronic insomnia and sleep therapy. *J Sleep Res*, 2008, 17: 335-343.
- Ashton, H. The diagnosis and management of benzodiazepine dependence. *Curr Opin Psychiat*, 2005, 18: 249-255.
- American Psychiatric Association. *DSM-IV: Diagnostic and Statistical Manual of Mental Disorders*, Washington DC, American Psychiatric Press, 1994.
- Barbone, F., McMahon, A. D., Davey, P. G., Morris, A. D., Reid, I. C., Mcdevitt, D. G. & Macdonald, T. M. Association of road-traffic accidents with benzodiazepine use. *Lancet*, 1998, 352: 1331-1336.
- Bastien, C. H., Leblanc, M., Carrier, J. & Morin, C. M. Sleep EEG power spectra, insomnia, and chronic use of benzodiazepines. *Sleep*, 2003, 26: 313-317.

CHAPTER 4

- Bateson, A. N. Basic pharmacologic mechanisms involved in benzodiazepine tolerance and withdrawal. *Curr Pharmaceut Des*, 2002, 8: 5-21.
- Beck, A. T., Ward, C. H., Mendelson, M., Mock, J. & Erbaugh, J. An inventory for measuring depression. *Arch Gen Psychiat*, 1961, 4: 561-571.
- Bond, A., & Lader, M. The use of analogue scales in rating subjective feelings. *Br J Med Psychol*, 1974, 47: 211-218.
- Brookhuis, K. A., De Waard, D. & Mulder, L. J. Measuring driving performance by car-following in traffic. *Ergonom*, 1994, 37: 427-434.
- Brouwer, W. H. Attention and driving: a cognitive neuropsychological approach. In Leclercq, M. & Zimmermann, P. (Eds.) *Applied Neuropsychology of Attention*. Hove, UK, Routledge, 2002.
- Buyse, D. J., Reynolds, C. F., 3rd, Monk, T. H., Berman, S. R. & Kupfer, D. J. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiat Res*, 1989, 28: 193-213.
- Carskadon, M.A., Dement, W.C., Mitler, M.M., Guilleminault, C., Zarcone, V.P. & Spiegel, R. Self-reports versus sleep laboratory findings in 122 drug-free subjects with complaints of chronic insomnia. *Am J Psychiat*, 133: 1382-1388.
- Chambers, M. J. & Keller, B. Alert insomniacs: Are they really sleep deprived? *Clin Psychol Rev*, 1993, 13: 649-666.
- De Gier, J. J., Alvarez, F. J., Mercier-Guyon, C. & Verstraete, A. G. Prescribing and dispensing guidelines for medicinal drugs affecting driving performance. In Verster, J. C., Pandi-Perumal, S. R., Ramaekers, J. G. & De Gier, J. J. (Eds.) *Drugs, Driving and Traffic Safety*. Basel, Switzerland, Birkhäuser Verlag, 2009.
- Derogatis, L. R. *The SCL-90-R: Administration, Scoring and Procedures Manual II*, Baltimore, Baltimore Clinical Psychometric Research, 1983.
- Dinges, D. F. & Powell, J. W. Microcomputer analyses of performance on a portable, simple visual RT task during sustained operations. *Behav Res Method Instrum Comp*, 1985, 17: 652-655.
- Dubois, S., Bedard, M. & Weaver, B. The impact of benzodiazepines on safe driving. *Traff Injury Prev*, 2008, 9: 404-413.

- Edinger, J. D., Fins, A. I., Sullivan, R. J., Jr., Marsh, G. R., Dailey, D. S., Hope, T. V., Young, M., Shaw, E., Carlson, D. & Vasilas, D. Do our methods lead to insomniacs' madness?: Daytime testing after laboratory and home-based polysomnographic studies. *Sleep*, 1997, 20: 1127-34.
- Edinger, J. D., Glenn, D. M., Bastian, L. A., Marsh, G. R., Dailey, D., Hope, T. V., Young, M., Shaw, E. & Meeks, G. Daytime testing after laboratory or home-based polysomnography: comparisons of middle-aged insomnia sufferers and normal sleepers. *J Sleep Res*, 2003, 12: 43-52.
- Fulda, S. & Schulz, H. Cognitive dysfunction in sleep disorders. *Sleep Med Rev*, 2001, 5: 423-445.
- Hartgerink-Lutgens, I., Vermeeren, A., Vuurman, E. & Kremer, B. Disturbed cognitive functions after nasal provocation in patients with seasonal allergic rhinitis. *Clin Exp Allergy*, in press.
- Hemmelgarn, B., Suissa, S., Huang, A., Boivin, J. F. & Pinard, G. Benzodiazepine use and the risk of motor vehicle crash in the elderly. *JAMA*, 1997, 278: 27-31.
- Höppener, P., Knottnerus, J. A., Metsemakers, J. F. M., Kocken, R. J. J. & Limonard, Ch. B. G. Het Registratienet Huisartsenpraktijken van de Rijksuniversiteit Limburg. Een geautomatiseerd steekproefbestand voor huisartsgeneeskundig onderzoek. *Huisarts Wet*, 1990, 33: 66-69.
- Iber, C., Ancoli-Israel, S., Chesson, A. & Quan, S. F. The AASM manual for the scoring of sleep and associated events: rules, terminology and technical specifications. American Academy of Sleep Medicine. Westchester, Ill, 2007.
- Jex, H. R., McDonnell, J. D. & Phatak, A. V. A "critical" tracking task for man-machine research related to the operator's effective delay time. I. Theory and experiments with a first-order divergent controlled element. NASA CR-616. *NASA Contract Rep NASA CR*, 1966: 1-105.
- Kindermann, S. S. & Brown, G. G. Depression and memory in the elderly: a meta-analysis. *J Clin Exp Neuropsychol*, 1997, 19: 625-642.

CHAPTER 4

- Kizilbash, A. H., Vanderploeg, R. D. & Curtiss, G. The effects of depression and anxiety on memory performance. *Arch Clin Neuropsychol*, 2002, 17: 57-67.
- Leufkens, T. R. M., Lund, J. S. & Vermeeren, A. Highway driving performance and cognitive functioning the morning after bedtime and middle-of-the-night use of gaboxadol, zopiclone and zolpidem. *J Sleep Res*, in press.
- Leufkens, T. R. M. & Vermeeren, A. Highway driving in elderly the morning after bedtime use of hypnotics: a comparison between temazepam 20 mg, zopiclone 7.5 mg and placebo. *J Clin Psychopharmacol*, in press.
- Logan, G. D., Cowan, W. B. & Davis, K. A. On the ability to inhibit simple and choice reaction time responses: a model and a method. *J Exp Psychol Hum Percept Perform*, 1984, 10: 276-291.
- Metsemakers, J. F. M., Höppener, P., Knottnerus, J. A., Kocken, R. J. J. & Limonard, Ch. B. G. Computerized health information in the Netherlands: a registration network of family practices. *Br J Gen Pract*, 1992, 42:102-106.
- Morin, A. K., Jarvis, C. I. & Lynch, A. M. Therapeutic options for sleep-maintenance and sleep-onset insomnia. *Pharmacother*, 2007, 27: 89-110.
- Morin, C. M., Leblanc, M., Daley, M., Gregoire, J. P. & Merette, C. Epidemiology of insomnia: Prevalence, self-help treatments, consultations, and determinants of help-seeking behaviors. *Sleep Med*, 2006, 7: 123-30.
- Moskowitz, H. Proceedings: Psychological tests and drugs. *Pharmakopsychiat Neuro Psychopharmacol*, 1973, 6: 114-26.
- Mulder-Hajonides Van Der Meulen, W. R. E. H. *Measurement of subjective sleep quality*, Amsterdam, Elsevier, 1981.
- Neutel, I. Benzodiazepine-related traffic accidents in young and elderly drivers. *Hum Psychopharmacol Clin Exp*, 1998, 13: S115-S123.
- O'Hanlon, J. F. Driving performance under the influence of drugs: rationale for, and application of, a new test. *Br J Clin Pharmacol*, 1984, 18 Suppl 1: 121s-129s.

- Ohayon, M. M. Epidemiology of insomnia: what we know and what we still need to learn. *Sleep Med Rev*, 2002, 6: 97-111.
- Orff, H. J., Drummond, S. P. A., Nowakowski, S. & Perlis, M. L. Discrepancy between subjective symptomatology and objective neuropsychological performance in insomnia. *Sleep*, 2007, 30: 1205-1211.
- Paterniti, S., Dufouil, C. & Alperovitch, A. Long-term benzodiazepine use and cognitive decline in the elderly: the Epidemiology of Vascular Aging Study. *J Clin Psychopharmacol*, 2002, 22: 285-293.
- Philip, P., Taillard, J., Sagaspe, P., Valtat, C., Sanchez-Ortuno, M., Moore, N., Charles, A. & Bioulac, B. Age, performance and sleep deprivation. *J Sleep Res*, 2004, 13: 105-110.
- Ramaekers, J. G. & O'Hanlon, J. F. Acrivastine, terfenadine and diphenhydramine effects on driving performance as a function of dose and time after dosing. *Eur J Clin Pharmacol*, 1994, 47: 261-266.
- Ray, W. A., Fought, R. L. & Decker, M. D. Psychoactive drugs and the risk of injurious motor vehicle crashes in elderly drivers. *Am J Epidemiol*, 1992, 136: 873-883.
- Rey, A. *L'examen clinique en psychologie.*, Paris, Presses Universitaires de France, 1964.
- Riedel, B. W. & Lichstein, K. L. Insomnia and daytime functioning. *Sleep Med Rev*, 2000, 4: 277-298.
- Riss, J., Cloyd, J., Gates, J. & Collins, S. Benzodiazepines in epilepsy: pharmacology and pharmacokinetics. *Acta Neurolog Scand*, 2008, 118: 69-86.
- Sagberg, F. Driver health and crash involvement: a case-control study. *Acc Anal Prev*, 2006, 38: 28-34.
- Smets, E. M., Garssen, B., Bonke, B. & De Haes, J. C. The Multidimensional Fatigue Inventory (MFI) psychometric qualities of an instrument to assess fatigue. *J Psychosom Res*, 1995, 39: 315-325.
- Spielberger, C. D., Gorsuch, R. L., Lushene, R. E., Vagg, P. R. & Jacobs, A. G. *Manual for the State-Trait Anxiety Inventory (Form Y)*, Palo Alto, Consulting Psychologists Press, Inc., 1983.

CHAPTER 4

- Stewart, R., Besset, A., Bebbington, P., Brugha, T., Lindesay, J., Jenkins, R., Singleton, N. & Meltzer, H. Insomnia comorbidity and impact and hypnotic use by age group in a national survey population aged 16 to 74 years. *Sleep*, 2006, 29: 1391-1397.
- Van Diest, R., Milius, H., Markusse, R. & Snel, J. The Sleep-Wake Experience List. *Tijdsch Soc Gezondheidsz*, 1989, 67: 343-347.
- Varkevisser, M. & Kerkhof, G. A. Chronic insomnia and performance in a 24-h constant routine study. *J Sleep Res*, 2005, 14: 49-59.
- Veldhuijzen, D. S., Van Wijck, A. J. M., Wille, F., Verster, J. C., Kenemans, J. L., Kalkman, C. J., Olivier, B. & Volkerts, E. R. Effect of chronic nonmalignant pain on highway driving performance. *Pain*, 2006, 122: 28-35.
- Vermeeren, A. Residual effects of hypnotics: epidemiology and clinical implications. *CNS Drugs*, 2004, 18: 297-328.
- Vermeeren, A., Danjou, P. E. & O'Hanlon, J. F. Residual effects of evening and middle-of-the-night administration of zaleplon 10 and 20 mg on memory and actual driving performance. *Hum Psychopharmacol*, 1998, 13: S98-S107.
- Vermeeren, A., O'Hanlon, J. F., Declerck, A. C., & Kho, L. Acute effects of zolpidem and flunitrazepam on sleep, memory and driving performance, compared to those of partial sleep deprivation and placebo. *Acta Ther*, 1995, 21: 47-64.
- Vermeeren, A., Riedel, W. J., Van Boxtel, M. P., Darwish, M., Paty, I. & Patat, A. Differential residual effects of zaleplon and zopiclone on actual driving: a comparison with a low dose of alcohol. *Sleep*, 2002, 25: 224-231.
- Verster, J. C., Volkerts, E. R., Olivier, B., Johnson, W. & Liddicoat, L. Zolpidem and traffic safety - the importance of treatment compliance. *Curr Drug Saf*, 2007, 2: 220-226.
- Verster, J. C., Volkerts, E. R., Schreuder, A. H., Eijken, E. J., Van Heuckelum, J. H., Veldhuijzen, D. S., Verbaten, M. N., Paty, I., Darwish, M., Danjou, P. & Patat, A. Residual effects of middle-of-the-night administration of

- zaleplon and zolpidem on driving ability, memory functions, and psychomotor performance. *J Clin Psychopharmacol*, 2002, 22: 576-583.
- Vignola, A., Lamoureux, C., Bastien, C. H. & Morin, C. M. Effects of chronic insomnia and use of benzodiazepines on daytime performance in older adults. *J Gerontol*, 2000, 55: 54-62.
- Wechsler, D. *Wechsler Adult Intelligence Scale - Revised manual*, New York, Psychological Corporation, 1981.
- Wingen, M., Ramaekers, J. G. & Schmitt, J. A. Driving impairment in depressed patients receiving long-term antidepressant treatment. *Psychopharmacol*, 2006, 188: 84-91.
- Wolschrijn, H., De Gier, J. J. & De Smet, P. A. G. M. Drugs and driving: a new categorization system for drugs affecting psychomotor performance. Maastricht, Institute for drugs, safety and behaviour, University of Limburg, 1991.
- Zijlstra, F. R. H. Efficiency in work behavior. A design approach for modern tools. Delft, Delft University of Technology, 1993.

CHAPTER 4

CHAPTER 5

Residual effects of zopiclone 7.5 mg on highway driving performance in elderly insomnia patients: a placebo controlled crossover study

Leufkens TRM, Ramaekers JG, de Weerd AW, Riedel WJ, Vermeeren A.

ABSTRACT

Residual effects of hypnotics on actual driving performance have been mainly determined in studies using a standardized driving test with healthy good sleepers. Responses to these effects may differ, however, between insomniacs and healthy volunteers due to the underlying sleep disorder. Performance in insomniacs is expected to improve due to the sleep improving effects of hypnotics and may attenuate the impairing effects. In addition, a majority of insomniacs uses hypnotics chronically resulting in the development of tolerance to impairing effects. Impaired driving performance in healthy volunteers may then be an overestimation of the actual effects in insomniacs.

The present study aims to compare the residual effects of the frequently prescribed hypnotic zopiclone 7.5 mg on driving performance of 16 elderly insomniacs chronically using hypnotics (frequent users), 16 elderly insomniacs not or infrequently using hypnotics (infrequent users) and 16 healthy, age matched, good sleepers (controls).

The study was conducted according to a 3x2 double-blind, placebo controlled crossover design, with three groups and two treatment conditions. Treatments were single oral doses of zopiclone 7.5 mg and placebo administered immediately before retiring to bed at 23:30 hours. Between 10 and 11 hours after administration subjects performed a standardized highway driving test.

Results indicated that zopiclone 7.5 mg significantly impaired driving performance in both insomnia groups and healthy controls. The magnitude of impairment was, however, significantly less in the frequent users group as compared with the controls. Effects found in the infrequent users were in line with previous studies, suggesting that these studies are able to validly predict the residual effects of hypnotics in insomnia patients who do not or infrequently use hypnotics.

INTRODUCTION

Residual daytime sedation is one of the main problems associated with hypnotic drug use. Experimental studies have demonstrated that the sedative actions of hypnotics impair psychomotor and cognitive functioning the morning after evening administration (Vermeeren, 2004). The related reduced alertness and slowed reactions are a particular problem for individuals who have to drive a car the morning following an evening dose. Epidemiological studies have shown that use of benzodiazepines, as well as zopiclone, is associated with an increased risk of car accidents (Hemmelgarn et al., 1997, Barbone et al., 1998, Neutel, 1998, Glass et al., 2005).

The severity and duration of residual effects on actual driving performance of hypnotics have been determined in experimental studies using a standardized driving test (cf. Vermeeren, 2004). Most of those studies have been conducted in healthy volunteers rather than in the target population, i.e. patients suffering from insomnia. Responses to the residual effects of hypnotics, however, may differ between insomnia patients and healthy good sleepers due to the underlying sleep disorder. In insomnia patients, hypnotics are expected to improve sleep and, as a consequence, they are expected to improve daytime performance as well. This improvement is supposed to attenuate or even compensate for the impairing effects of hypnotics. In addition, the majority of insomnia patients use hypnotics for prolonged periods (Curran et al., 2003), which may result in the development of tolerance to the impairing effects. Impaired driving performance found in healthy medication naïve volunteers may then be an overestimation of the actual effects in insomnia patients.

To date, there is a lack of experimental studies that assess driving performance following hypnotic administration in insomnia patients. Moreover, the residual effects of hypnotics on driving have not yet been directly compared between insomnia patients and healthy good sleepers. In a previous study, we explored driving performance between insomnia patients who used their own prescribed hypnotics, insomnia patients who did not use hypnotics and healthy, good sleepers and found that performance was not significantly different

between insomnia patients and healthy controls (Leufkens et al., in prep.). In addition, there were no significant differences between insomnia patients who chronically used hypnotics and patients who used hypnotics infrequently. A limitation of that study was that the frequent users group used a variety of hypnotic drugs most of which were not expected to produce residual sedation at all. In addition, differences in dose and half-life may have added to the absence of any performance impairment. In order to determine to what extent residual effects of hypnotics on driving performance are reduced by tolerance in insomnia patients, the impairing effects of a hypnotic known to produce residual sedation should be compared between chronic users of hypnotics and healthy controls. If tolerance develops, the residual impairment should be less in chronic users compared to controls. A reduction in residual impairment in insomnia patients chronically using hypnotics may also be due to the drug's therapeutic effects on sleep, however. Therefore, residual impairment should also be compared between healthy controls and insomnia patients who do not or infrequently use hypnotics. The latter are not expected to develop tolerance and should therefore only show a potential reduction in impairment due to improved sleep.

The present study aims to compare the residual effects of the frequently prescribed hypnotic zopiclone 7.5 mg on driving performance of 16 insomnia patients who chronically use hypnotics, 16 insomnia patients who do not or infrequently use hypnotics and 16 healthy, age matched, good sleepers.

METHODS

Subjects

All subjects in the present study participated in a previous study by Leufkens et al. (Leufkens et al., in prep.). They were asked upon completion of the former study to continue their participation in the present study. In the previous study, insomnia patients, in the age range of 52 to 73 years, were initially recruited through a network of local general practitioners in the region of Maastricht, The Netherlands (Regionaal Netwerk Huisartsen, RNH). Possible candidates were

selected from a computerized database of the Center for Data and Information Management of Maastricht University (MEMIC). This recruitment procedure was subsequently backed up by advertisement in local newspapers. Healthy controls were recruited by advertisements in local newspapers.

Three groups of 16 subjects, ranging from 52 to 71 years of age, participated in the present study. Groups were 16 individuals with insomnia who chronically used hypnotics ('frequent users'; 7 female and 9 male), 16 individuals with insomnia who did not or infrequently used hypnotics ('infrequent users'; 8 female and 8 male) and 16 self-defined good sleepers, matched for age and driving experience ('controls'; 7 female and 9 male). Their mean (\pm SD) ages were 62.6 (4.5) for the frequent users insomnia group, 62.3 (6.2) for the infrequent users group and 62.9 (4.3) for the control group.

Insomnia patients had to meet the inclusion criteria for primary insomnia according to DSM-IV (APA, 1994): (i) subjective complaints of insomnia, defined as difficulties initiating sleep (sleep latency >30 min) and/or maintaining sleep (awakenings >30 min); (ii) duration of more than 1 month; (iii) the sleep disturbance causes clinically significant distress or impairment; (iv) insomnia does not occur exclusively during the course of a mental disorder and (v) insomnia is not due to another medical or sleep disorder or effects of medication or drug abuse.

Sleep complaints were measured using Dutch versions of the Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989), the Sleep Wake Experience List (SWEL) (van Diest et al., 1989) and the general version of the Groningen Subjective Quality of Sleep questionnaire (GSQS-gen) (Mulder-Hajonides van der Meulen, 1981). Additionally, a daily journal and the specific version of the Groningen Subjective Quality of Sleep questionnaire (GSQS-spec) (Mulder-Hajonides van der Meulen, 1981) were completed upon arising each morning for two weeks providing subjective estimates of sleep quality.

Insomnia patients were assigned to the 'frequent users' group when they used a benzodiazepine, zopiclone or zolpidem as sleeping medication for at least four nights per week during the previous three months or more. The average (\pm SD) nightly use of hypnotics in the frequent users group was 6.6

(1.0) nights per week. The average (\pm SD) duration of their hypnotic use was 7.1 (5.0) years. Patients not using hypnotics or using hypnotics less than or equal to three days per week were assigned to the 'infrequent users' group. Their average (\pm SD) nightly use of hypnotics was 4.5 (3.2) night per month and their average (\pm SD) duration of use was 7.8 (8.1) years. Self-defined good sleepers did not meet any of the criteria for insomnia and did not use any hypnotics.

All participants had to meet the following inclusion criteria: possession of a valid driving license for at least three years; average driving experience of at least 3000 km per year over the last three years; mentally and physically fit to drive; good health based on a pre-study physical examination, medical history, vital signs, electrocardiogram, blood biochemistry, haematology, serology and urinalysis; body mass index (BMI) between 19 and 30 kg/m².

Exclusion criteria were history of drug or alcohol abuse; presence of a significant medical, neurological, psychiatric disorder, or sleep disorder other than insomnia; chronic use of medication that affects driving performance, except hypnotics; drinking more than 6 cups of coffee per day; drinking more than 21 alcohol containing beverages per week; smoking more than 10 cigarettes per day.

Participants were screened for major psychopathology by use of the Symptom Checklist 90 Revised (SCL-90-R) (Derogatis, 1983), the Beck Depression Inventory (BDI) (Beck et al., 1961), the State-Trait Anxiety Inventory (STAI) (Spielberger et al., 1983) and the Multidimensional Fatigue Inventory (MFI) (Smets et al., 1995).

During participation use of caffeine was prohibited from 8 hrs prior to arrival on test days, until discharge the next morning. Alcohol intake was not allowed from 24 hours prior to each dosing until discharge. Smoking was prohibited from 1 hr prior to bedtime until discharge.

In order to minimize withdrawal symptoms during the placebo night, patients assigned to the 'frequent users' group were instructed to discontinue their hypnotic intake three nights before each treatment period. Frequent users who expected difficulties during the three hypnotic-free nights were provided escape medication, consisting of zolpidem at a maximum of 1 dose of 10 mg per night,

to be used only in case of intolerable withdrawal effects. Zolpidem 10 mg was selected to limit variability in hypnotic drugs used and because it is known to be free from residual effects when taken at bedtime before 8 hours of sleep (Vermeeren, 2004).

The study was conducted in accordance with the code of ethics on human experimentation established by the World Medical Association's Declaration of Helsinki (1964) and amended in Edinburgh (2000). The protocol was approved by the medical ethics committee of Maastricht University and University Hospital of Maastricht. Subjects were explained the aims, methods, and potential hazards of the study and they signed a written informed consent prior to any study-related assessments.

Design and treatments

The study was conducted according to a 3x2 double-blind, placebo controlled crossover design, with three groups (16 insomnia patients chronically using hypnotics, 'frequent users'; 16 insomnia patients not or infrequently using hypnotics, 'infrequent users'; and 16 self-defined good sleepers, matched for age and driving experience, 'controls') and two treatment conditions. Treatments were single oral doses of zopiclone 7.5 mg and placebo administered in identical looking capsules and ingested immediately before retiring to bed at 23:30 hours. Treatments orders were balanced within groups (placebo – zopiclone or vice versa). Washout periods between treatments were at least one week.

Assessments

Sleep

Sleep during treatment nights was evaluated objectively by polysomnography (to be described in a subsequent paper) and subjectively by completing the specific version of the Groningen Subjective Quality of Sleep Scale (GSQS-spec) upon arising. The GSQS-spec provides subjective evaluation of number of sleep complaints; sleep onset latency (in min); total sleep time (in min); early morning awakening (in min); and number of awakenings.

Driving performance

Driving performance was assessed using two on-the-road driving tests, a highway driving test and a car following test (to be described in a subsequent paper). The Highway Driving Test (O'Hanlon, 1984) measures road tracking performance that is mainly determined by the delay lag between sensory information, execution of motor reaction and the vehicle's dynamic response. In this test, subjects operate a specially instrumented vehicle over a 100 km (61 mi) primary highway circuit, accompanied by a licensed driving instructor having access to dual controls. The subjects' task is to maintain a constant speed of 95 km/h (58 mi/h) and a steady lateral position between the delineated boundaries of the slower traffic lane. The vehicle speed and lateral position are continuously recorded. These signals are edited off line to remove data recorded during overtaking maneuvers or disturbances caused by roadway or traffic situations. The remaining data are then used to calculate means and standard deviations of lateral position and speed. Standard deviation of lateral position (SDLP in centimeters) is the primary outcome variable. SDLP is a measure of road tracking error or 'weaving'. The test duration is approximately 1 hour.

Cognitive and psychomotor performance

Cognitive and psychomotor performance was assessed by use of a battery of laboratory tests for word learning, digit span, critical tracking, divided attention, psychomotor vigilance and inhibitory control. Tests were previously proven to be sensitive to daytime sleepiness or sedation due to use of hypnotics (Vermeeren et al., 1995, Vermeeren et al., 1998, Vermeeren et al., 2002, Verster et al., 2002, Vermeeren, 2004, Leufkens et al., in press, Leufkens and Vermeeren, in press) or insomnia (Fulda and Schulz, 2001). This paper focuses on the word learning test and the psychomotor vigilance test.

The Word Learning Test (Rey, 1964) is a verbal memory test for the assessment of immediate recall, delayed recall and recognition performance. Fifteen monosyllabic nouns are presented and at the end of the sequence the subject is asked to recall as many words as possible. This procedure is

repeated five times and after a delay of at least 30 minutes the subject is again required to recall as many words as possible. At this trial the nouns are not presented. Finally, a sequence of 30 monosyllabic nouns is presented, containing 15 nouns from the original set and 15 new nouns in random order. The subject has to indicate whether a noun originates from the old set or it is from a new set of nouns.

The Psychomotor Vigilance Task (Dinges and Powell, 1985) is based on a simple visual RT test. Subjects are required to respond to a visual stimulus presented at variable interval (2000 to 10000 msec) by pressing either the right or the left button with the dominant hand. The visual stimulus is a counter turning on and incrementing from 0 to 60 sec at 1-msec intervals. In response to the subject's button press, the counter display stops incrementing, allowing the subject 1 sec to read the RT before the counter restarts. If a response has not been made in 60 sec, the clock resets and the counter restarts.

Subjective evaluation

Subjective evaluations of mood, sedation and driving quality were assessed using a series of visual analogue scales (100 mm). The subjects were instructed to rate their subjective feelings using a 16-item mood scale which provides three factor analytically defined summary scores for 'alertness', 'contentedness', and 'calmness' (Bond and Lader, 1974).

Subjective feelings of daytime sleepiness were rated with the Karolinska Sleepiness Scale (Akerstedt and Gillberg, 1990). Scores on this scale range from 1 (extremely alert) to 9 (very sleepy, fighting sleep).

Subjects rated the degree of effort they had to put in driving performance using the Rating Scale Mental Effort (Zijlstra, 1993). The scale is a visual analogue scale (150 mm) with additional verbal labels. In addition, subjects rated the extent of influence of the drug on their driving performance, prior to and upon completion of the Highway Driving Test, using a 100 mm visual analogue scale.

The driving instructors rated each subject's driving quality and apparent sedation at the conclusion of the Highway Driving Test, using two 100 mm visual analogue scales.

Procedure

Subjects were individually trained to perform the laboratory tests during two sessions of approximately 1.5 hrs in a previous study (Leufkens et al., in prep.). In that study, they underwent two nights of sleep evaluation in that study. Subjects were therefore sufficiently familiarized with the testing facilities and procedures.

Treatment periods started in the evening of Day 1, when the subjects arrived at the site at approximately 20:00 hours, and lasted until Day 2, when they were transported home after the driving test, at approximately 11:45 hours. On arrival at the sleeping facility in each treatment period, subjects' eligibility was verified. They were questioned about adverse events and use of medication since their last visit. Hereafter, electrodes for polysomnographic recording were attached.

Subjects ingested their medication and retired to bed at 23:30 hrs. They were awakened at 07:30 hrs and served a light standardized breakfast. At 08:00 hrs (i.e. 8.5 hrs post dose) they filled out the subjective rating scales for sleep, mood, and daytime sleepiness, and started the laboratory tests. At approximately 9:00 hrs a blood sample was taken. Subjects were subsequently transported to the start of the highway driving test. Before driving they rated the anticipated effect of the drug on their driving performance, and performed the highway driving test between 09:30 and 10:30 hrs (i.e. 10:00 – 11:00 hrs post-dose). Upon completion subjects were asked to rate the mental effort it took to perform the driving test and to evaluate the influence of the drug on their driving performance. Next, subjects performed the car following test, after which they returned to the testing facilities for removal of the electrodes.

Statistical analysis

Sample size was based on a power calculation for detecting a clinically relevant effect of 2.4 cm in the primary measure of this study, the SDLP. This change

corresponds to the effects of alcohol on SDLP, while blood alcohol concentrations (BACs) are 0.5 g/L as measured in a previous study (Louwerens et al., 1987). Given a test-retest reliability of SDLP of at least $r=0.70$, a group of 16 subjects should permit detection of a mean change in SDLP of 2.0 cm, with a power of at least 90% and an α risk of 0.05.

Overall effects were analyzed using a mixed model analysis of variance with *Group* as between subject factor with three levels ('frequent users', 'infrequent users', 'controls') and *Treatment* as within subjects factor with two levels (zopiclone, placebo). Significant ($p<0.05$) main effects or interactions were further analyzed using three univariate comparisons between groups for each treatment, and paired t-tests between placebo and zopiclone within each group.

All statistical analyses were done by using the Statistical Package for the Social Sciences (SPSS) statistical program (version 15.0 for Windows; SPSS, Chicago, IL).

RESULTS

Highway Driving Test

Out of 96 driving tests, one was terminated before scheduled completion because the driving instructor judged that it would be unsafe to continue. The subject was a female insomnia patient from the infrequent users group who had been administered. Her Standard Deviation of Lateral Position (SDLP) score was calculated from the data collected until termination of the ride.

Figure 1 presents mean \pm SE SDLP values recorded after placebo and zopiclone 7.5 mg for each group separately.

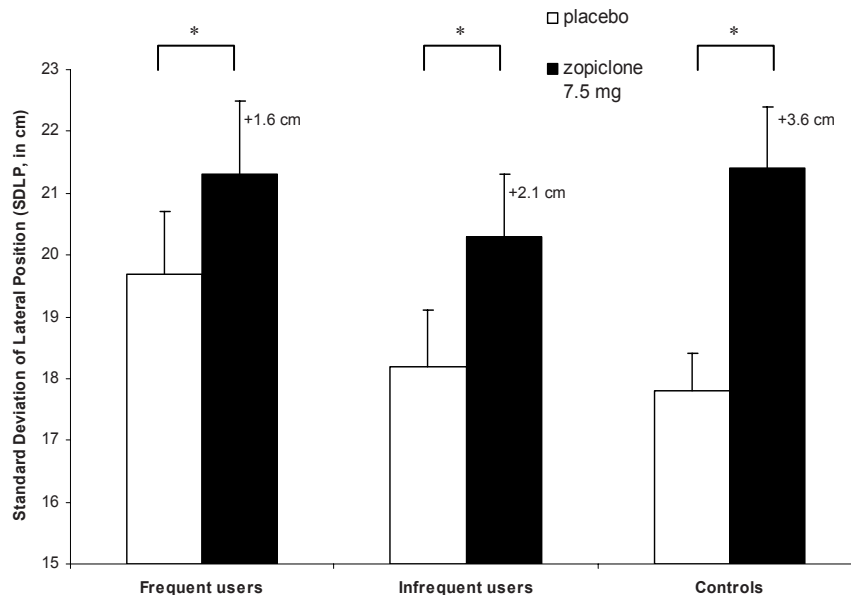


Figure 1. Mean (+SE) SDLP for each group separately (* = significant drug effect; $p < 0.05$)

Analysis showed a highly significant overall Treatment effect on SDLP ($F_{1,45}=33.86$, $p < 0.001$). Zopiclone significantly impaired driving in all groups. Compared to placebo the increase in SDLP was +1.6 cm ($p=0.010$) in the frequent users group, +2.1 cm ($p=0.020$) in the infrequent users group and +3.6 cm ($p < 0.001$) in the healthy control group. T-tests for independent samples showed that the mean increase in SDLP from placebo to zopiclone was significantly lower in the frequent users group than the control group ($p=0.045$). There was no difference between the infrequent users and controls and between the two insomnia groups. In addition, no differences were found between the groups in SDLP after placebo administration.

Standard Deviation of Speed (table 1) showed a significant main effect of treatment ($F_{1,45}=12.24$, $p=0.001$) and a treatment by group interaction ($F_{2,45}=3.42$, $p=0.041$).

Overall, zopiclone significantly impaired subjects control over speed variability. Paired t-tests showed that zopiclone significantly increased SDSP in the control group ($p < 0.004$) and the frequent users group ($p=0.009$), but not in the

infrequent users group. There was no significant difference between groups in SDSP.

Table 1. Mean (\pm SE) scores of driving test and subjective evaluations for each condition and group separately

		Group			Statistics (p-values)		
Variable	Treatment	Frequent users	Infrequent users	Controls	Drugx Group	Drug	Group
<i>Highway Driving Test</i>							
SDLP (cm)	placebo	19.7 (1.0)	18.2 (0.9)	17.8 (0.6)	NS	<.001	NS
	zopiclone	21.3 (1.2) ^a	20.3 (1.0) ^a	21.4 (1.0) ^a			
SDSP (km/h)	placebo	2.2 (0.1)	2.3 (0.2)	2.1 (0.1)	.041	.001	NS
	zopiclone	2.5 (0.2) ^a	2.4 (0.1)	2.5 (0.4) ^a			
<i>Subjective Evaluations by Driving Instructors</i>							
Driving Quality	placebo	58.4 (5.8)	58.8 (4.6)	59.2 (5.0)	NS	NS	NS
	zopiclone	58.6 (4.7)	61.1 (4.5)	55.8 (3.8)			
Apparent Sedation	placebo	18.9 (5.4)	15.1 (5.0)	18.4 (6.0)	NS	NS	NS
	zopiclone	23.4 (4.3)	21.8 (3.2)	21.8 (4.4)			
<i>Subjective Evaluations by Participants</i>							
Anticipated Driving Quality	placebo	71.7 (5.6)	73.6 (4.8)	86.2 (3.5)	NS	.017	NS
	zopiclone	67.6 (6.2)	71.7 (5.9)	66.4 (5.5) ^a			
Experienced Driving Quality	placebo	67.9 (4.9)	65.0 (4.5)	78.3 (4.3)	NS	.020	NS
	zopiclone	60.8 (5.4)	62.4 (6.1)	66.8 (5.8) ^a			
Mental Effort	placebo	31.4 (5.3)	35.4 (5.4)	24.8 (4.7)	NS	<.001	NS
	zopiclone	45.1 (8.9)	53.3 (7.9) ^a	45.1 (6.8) ^a			

^a = Significant *Drug* effect ($p < .05$)

Subjective evaluations of driving performance

Mean \pm SE scores of the subjective evaluations of driving performance are presented in table 1. The driving instructors did not judge the subjects' driving quality and appearance of being sedated to be significantly different between zopiclone and placebo in all groups.

Overall, subjects' ratings of anticipated and experienced driving quality were lower after zopiclone as compared to placebo (anticipated: $F_{1,44}=6.14$, $p=0.017$; experienced: $F_{1,44}=5.79$, $p=0.020$). Paired t-tests showed that these differences reached significance within the control group, but not in the patient groups. Healthy controls expected driving quality to be worse after zopiclone administration ($p=0.006$) and they confirmed this expectation after the driving

test ($p=0.013$). Changes in the patient groups were in the same direction, but smaller. In the placebo condition, t-tests for independent samples revealed that both insomnia groups rated their driving quality significantly lower than the control group (frequent users: $p=0.040$; infrequent users: $p=0.045$).

Overall, subjects' perceived mental effort to perform the driving test was increased after zopiclone as compared to placebo ($F_{1,45}=16.15$, $p<0.001$). Paired t-tests showed that this difference reached significance within the control group ($p=0.009$) and the infrequent users group ($p=0.008$), but not in the frequent users group. Differences between groups were not significant.

Cognitive and psychomotor assessment

Table 2 summarizes the mean \pm SE scores of the Word Learning Test and the Psychomotor Vigilance Task.

Overall, zopiclone impaired all parameters of the Word Learning Test, i.e. immediate recall ($F_{1,45}=9.78$, $p=0.003$), delayed recall ($F_{1,45}=5.49$, $p=0.024$), recognition score ($F_{1,45}=6.48$, $p=0.014$), and recognition reaction time ($F_{1,45}=8.50$, $p=0.006$). Paired t-tests revealed that these effects generally did not reach significance in each group separately, except for the effect on immediate recall in the infrequent users group ($p=0.039$), and the effects on the recognition score in the control group ($p=0.045$). T-tests for independent samples revealed that the frequent users scored significantly worse than the healthy controls on the immediate recall score in the placebo condition ($p=0.020$). Other significant group differences were not found.

Performance in the Psychomotor Vigilance Task did not show significant differences between treatments and groups.

Table 2. Mean (\pm SE) scores of cognitive performance tests for each condition and group separately

Variable	Treatment	Group			Statistics (<i>p-values</i>)		
		Frequent users	Infrequent users	Controls	Drugx Group	Drug	Group
<i>Word Learning Test</i>							
Immediate Recall Score	placebo	39.5 (1.9)	43.6 (2.2)	46.2 (1.9)	NS	.003	NS
	zopiclone	35.4 (2.9)	39.1 (2.7) ^a	41.6 (2.5)			
Delayed Recall	placebo	5.3 (0.7)	6.8 (0.9)	7.3 (0.8)	NS	.024	NS
	zopiclone	4.8 (0.8)	5.8 (0.8)	5.4 (0.7)			
Recognition Score	placebo	25.4 (1.1)	25.0 (1.3)	25.5 (1.3)	NS	.014	NS
	zopiclone	24.4 (0.8)	23.4 (1.4)	23.5 (1.5) ^a			
Recognition Reaction Time (msec)	placebo	848 (32)	785 (36)	851 (33)	NS	.006	NS
	zopiclone	889 (39)	863 (40)	893 (34)			
<i>Psychomotor Vigilance Task</i>							
Average Reaction Time (msec)	placebo	290 (13)	290 (15)	281 (8)	NS	NS	NS
	zopiclone	288 (12)	303 (16)	297 (11)			
Lapses >500 msec	placebo	3.1 (1.0)	1.7 (0.4)	2.1 (0.6)	NS	NS	NS
	zopiclone	2.6 (0.8)	3.1 (1.0)	2.6 (0.6)			

^a = Significant *Drug* effect ($p < .05$)**Subjective evaluations of sleep quality**

Table 3 summarizes the mean \pm SE scores of the subjective sleep parameters for each group separately after administration of placebo and zopiclone.

Significant overall main effects of treatment and group were found for all parameters. In addition, significant interactions showed that the effect of zopiclone differed between groups in number of complaints, sleep onset time and total sleep time. Paired *t*-tests showed that in both insomnia groups number of sleep complaints was significantly reduced (both groups: $p < 0.001$) and total sleep time was significantly increased (frequent users: $p < 0.001$; infrequent users: $p = 0.001$) after zopiclone administration (figure 2). Number of awakenings was significantly reduced after zopiclone in all groups (frequent users: $p = 0.022$; infrequent users: $p < 0.001$; controls: $p = 0.008$). Sleep onset time was significantly diminished after zopiclone in the frequent users group only ($p = 0.014$).

Table 3. Mean (\pm SE) scores of subjective sleep quality, subjective sleepiness and subjective feelings upon arising

		Group			Statistics (p-values)		
Variable	Treatment	Frequent users	Infrequent users	Controls	Drugx Group	Drug	Group
<i>Groningen Subjective Quality of Sleep</i>							
Complaints	placebo	10.8 (0.8) ^b	8.9 (0.9) ^b	4.2 (1.0)	.022	<.001	<.001
	zopiclone	5.3 (1.0) ^{a, b}	3.3 (0.6) ^a	2.4 (0.5)			
Sleep Onset Time (min)	placebo	114 (22) ^{b, c}	53 (11)	36 (8)	.049	.001	<.001
	zopiclone	44 (11) ^a	27 (4)	24 (4)			
Total Sleep Time (min)	placebo	241 (21) ^b	291 (23) ^b	385 (13)	.012	<.001	<.001
	zopiclone	355 (18) ^{a, b, c}	403 (12) ^a	419 (8) ^a			
Awakenings	placebo	3.5 (0.6)	3.8 (0.6) ^b	2.0 (0.4)	NS	<.001	.027
	zopiclone	1.9 (0.4) ^{a, b}	1.4 (0.4) ^a	0.7 (0.2) ^a			
<i>Karolinska Sleepiness Scale</i>							
Subjective Sleepiness	placebo	5.1 (0.4) ^b	4.4 (0.5)	3.5 (0.3)	NS	NS	.009
	zopiclone	5.1 (0.4) ^b	4.6 (0.4)	3.7 (0.3)			
<i>Subjective Feelings</i>							
Alertness	placebo	58.8 (4.5) ^b	64.9 (4.1)	73.9 (3.4)	.013	NS	NS
	zopiclone	69.2 (3.9) ^a	65.8 (2.8)	66.2 (4.7) ^a			

^a = significant *Drug* effect ($p < .05$); ^b = significantly different from control group ($p < .05$); ^c = significantly different from infrequent users group ($p < .05$)

Differences between the frequent users and controls were found in number of complaints ($p < 0.001$), sleep onset time ($p = 0.006$) and total sleep time ($p < 0.001$) after placebo. Following zopiclone administration the frequent users reported significantly more sleep complaints ($p = 0.007$), shorter total sleep time ($p = 0.001$) and more awakenings ($p = 0.015$) than the controls.

Comparisons between the infrequent users and the controls revealed that there were significant differences in number of complaints ($p = 0.001$), total sleep time ($p = 0.001$) and number of awakenings ($p = 0.027$) after administration of placebo. Differences between the groups disappeared after zopiclone administration.

Comparisons between the insomnia groups showed that the frequent users had a significantly longer sleep onset time ($p = 0.006$) and a significantly shorter total sleep time ($p = 0.001$) than the infrequent users in the placebo condition. There were no differences between the insomnia groups after zopiclone administration.

ZOPICLONE 7.5 MG, DRIVING AND INSOMNIA PATIENTS

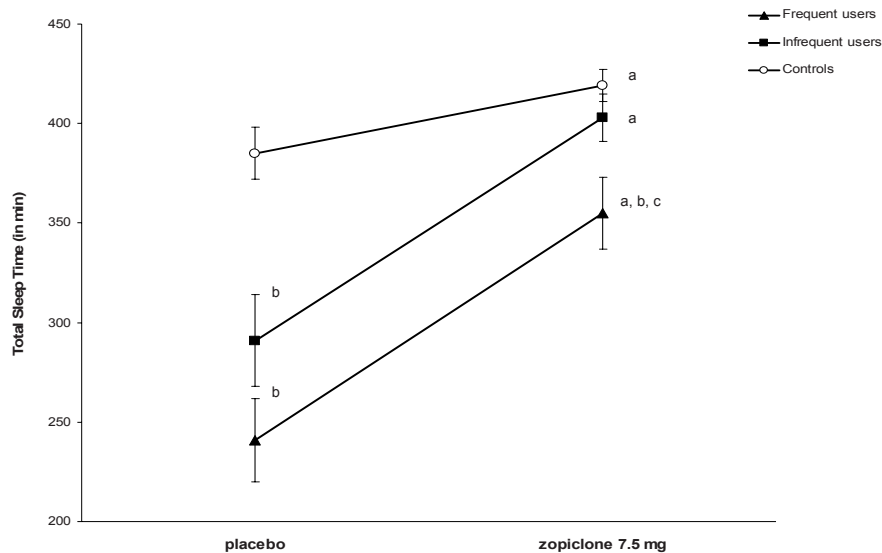


Figure 2. Mean (\pm SE) subjective total sleep time following placebo and zopiclone 7.5 mg administration, for each group separately. ^a = significant *Drug* effect ($p < .05$); ^b = significantly different from control group ($p < .05$); ^c = significantly different from infrequent users group ($p < .05$)

Subjective evaluations of sleepiness and feelings

Table 3 summarizes the mean \pm SE scores of the subjective evaluations of daytime sleepiness and mood for each group separately after administration of placebo and zopiclone.

Subjects' ratings of sleepiness as measured by the Karolinska Sleepiness Scale were significantly different between groups ($F_{2,44}=5.28$, $p=0.009$), but not between treatments. The frequent users group felt more sleepy than the healthy controls after placebo (0.003) and after zopiclone ($p=0.023$) administration.

Subjective feelings of alertness as measured by Bond and Lader's mood scale showed a significant treatment by group interaction ($F_{2,45}=4.81$, $p=0.013$). In the placebo condition, the insomnia groups felt significantly less alert than the control group. This difference was significant for the frequent users group ($p=0.011$). Use of zopiclone increased next day alertness in the frequent users ($p=0.029$), whereas it impaired alertness in the healthy controls ($p=0.040$).

DISCUSSION

Results of the present study show that a single oral dose of zopiclone 7.5 mg significantly impairs driving performance in insomnia patients who chronically use hypnotics, in insomnia patients who infrequently use hypnotics and in healthy, good sleepers at 10 to 11 hours after bedtime administration. The impairing effect of zopiclone on driving, as reflected by the rise in SDLP compared with placebo, was significantly different between the frequent users and the healthy controls. The effect found in the frequent users group (+1.6 cm) is on average of lesser magnitude than that produced by alcohol in a previous study while subjects drove with blood alcohol concentrations (BAC) of 0.5 mg/mL (+2.4 cm) (Louwerens et al., 1987), which is the legal limit for driving a car in most countries. In contrast, the increase of 3.6 cm in SDLP from placebo after zopiclone 7.5 mg administration in the healthy control group is above this effect of alcohol. Zopiclone produced an effect of +2.1 cm in the infrequent users group, which was slightly less than that of alcohol while BACs are 0.5 mg/mL. However, there was no statistical difference in effect of zopiclone between the infrequent users and the controls.

The significantly decreased magnitude of effect of zopiclone 7.5 mg on driving performance in the frequent users as compared to the healthy controls suggests that residual effects are attenuated by chronic use of hypnotics. This implicates that results from studies conducted with healthy volunteers appear to give an overestimation of the actual effects in insomnia patients chronically using hypnotics. It should be mentioned, however, that SDLP scores following zopiclone administration were still significantly increased in the frequent users group, indicating that residual effects do not completely disappear. Nonetheless, the difference in zopiclone's residual effects suggests at least partial tolerance in users. On the other hand, absolute scores of SDLP in the placebo condition were highest in the frequent users group, suggesting that the reduction in magnitude of effect in this group was due to an elevated SDLP in the placebo condition. These results suggest that withdrawal symptoms were still present despite discontinuation of own hypnotic intake three days before

each treatment period. The frequent users may therefore have experienced discomfort from the hypnotic free night which may have affected their driving performance. As a consequence, the elevated SDLP scores in the placebo condition may have reduced the effect of zopiclone on driving performance in this group.

The magnitude of residual effects of zopiclone 7.5 mg found in the infrequent users group is in line with previous studies conducted in healthy younger drivers (Vermeeren et al., 1998, Vermeeren et al., 2002, Leufkens et al., in press). In those studies, the mean increase in SDLP from placebo after zopiclone administration ranged from +2.5 cm to +4.9 cm. This suggests that the residual effects of hypnotics found in healthy volunteers can validly predict the effects in older patients suffering from insomnia.

The impairing effects on driving after zopiclone appeared not to be noticed by the patients themselves. Prior to the start of the driving test, they did not expect to drive differently after administration of zopiclone than after placebo. In addition, after completion of the test they did not rate their driving quality differently between zopiclone and placebo. In contrast, the healthy controls anticipated their driving quality to be significantly worse after zopiclone. Their expectations were confirmed after the test as they evaluated their driving quality significantly lower after zopiclone administration as compared with placebo.

Whereas the residual adverse effects of zopiclone remained undetected by the insomnia patients according to their subjective evaluations, opposite results were found for the evaluations of its therapeutic effects. Both insomnia groups reported significantly improved subjective sleep quality on most parameters after zopiclone administration as compared with placebo. The healthy controls, however, appeared to benefit considerably less from the sleep inducing properties of zopiclone. Furthermore, the frequent users group felt significantly more alert the morning after an evening dose of zopiclone than after placebo. The infrequent users did not report a difference in alertness, whereas the healthy controls reported feeling significantly less alert after zopiclone than after placebo.

The lack of awareness of residual sedative effects of zopiclone 7.5 mg may cause insomnia patients to believe that car driving is safe the morning after evening administration. Even more, these beliefs may be strengthened by the experienced improvement of subjective sleep quality and increased subjective alertness. These results stress, however, the importance of general physicians to warn their patients about the impairing effects of zopiclone 7.5 mg on driving performance.

The impairing effects of zopiclone on driving performance were corroborated by the results of the word learning test, as was shown by overall significant differences between placebo and zopiclone on all parameters. Evident impairing residual effects of zopiclone 7.5 mg on verbal learning have been found previously in studies comprising both healthy elderly and younger subjects (Leufkens et al., in press, Leufkens and Vermeeren, in press, Leufkens et al., in prep.).

Performance on the psychomotor vigilance task was, however, not different between placebo and zopiclone administration. Although there is ample evidence that the PVT is highly sensitive to the effects of sleep deprivation (Lim and Dinges, 2008), there seem to be almost no studies assessing effects of sedating drugs on this test. To our knowledge, the sedative residual effects of zopiclone 7.5 mg have not yet been investigated with use of this task. There is a recent study, however, showing significant effects of blood alcohol concentrations of 0.3 mg/mL on PVT performance in 18 healthy men (Howard et al., 2007). This suggests that the task should have been sufficiently sensitive to detect the residual effects of zopiclone, which were comparable in magnitude to those of blood alcohol concentrations of 0.5 mg/mL as measured by SDLP. The failure to find an effect on the PVT therefore suggests that performance on this test may be less sensitive to residual effects of GABAergic hypnotic drugs than acute effects of alcohol.

To summarize, results of the present study indicate that driving performance is moderately impaired in insomnia patients after evening administration of zopiclone 7.5 mg at least until 11 hours after intake. Chronic use of hypnotics seems to attenuate the severity of effects of zopiclone 7.5 mg. Nevertheless,

this reduction does not result in an absence of impairing effects in insomnia patients chronically using hypnotics. The magnitude of effects found in the infrequent users group was in line with previous studies investigating residual effects of zopiclone 7.5 mg in healthy, younger volunteers. This suggests that these studies are able to validly predict the residual effects of hypnotics in insomnia patients who do not use hypnotics.

REFERENCES

- Akerstedt, T. & Gillberg, M. Subjective and objective sleepiness in the active individual. *Internat J Neurosc*, 1990, 52: 29-37.
- American Psychiatric Association. *DSM-IV: Diagnostic and Statistical Manual of Mental Disorders*, Washington DC, American Psychiatric Press, 1994.
- Barbone, F., McMahon, A. D., Davey, P. G., Morris, A. D., Reid, I. C., Mcdevitt, D. G. & Macdonald, T. M. Association of road-traffic accidents with benzodiazepine use. *Lancet*, 1998, 352: 1331-1336.
- Beck, A. T., Ward, C. H., Mendelson, M., Mock, J. & Erbaugh, J. An inventory for measuring depression. *Arch Gen Psychiat*, 1961, 4: 561-571.
- Bond, A., & Lader, M. The use of analogue scales in rating subjective feelings. *Br J Med Psychol*, 1974, 47: 211-218.
- Buysse, D. J., Reynolds, C. F., 3rd, Monk, T. H., Berman, S. R. & Kupfer, D. J. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiat Res*, 1989, 28: 193-213.
- Curran, H. V., Collins, R., Fletcher, S., Kee, S. C., Woods, B. & Iliffe, S. Older adults and withdrawal from benzodiazepine hypnotics in general practice: effects on cognitive function, sleep, mood and quality of life. *Psychol Med*, 2003, 33: 1223-1237.
- Derogatis, L. R. *The SCL-90-R: Administration, Scoring and Procedures Manual II.*, Baltimore, Baltimore Clinical Psychometric Research, 1983.
- Dinges, D. F. & Powell, J. W. Microcomputer analyses of performance on a portable, simple visual RT task during sustained operations. *Behav Res Meth Instrum Comp*, 1985, 17: 652-655.

CHAPTER 5

- Fulda, S. & Schulz, H. Cognitive dysfunction in sleep disorders. *Sleep Med Rev*, 2001, 5: 423-445.
- Glass, J., Lanctot, K. L., Herrmann, N., Sproule, B. A. & Busto, U. E. Sedative hypnotics in older people with insomnia: meta-analysis of risks and benefits. *BMJ Clin Res*, 2005, 331: 1169-1175.
- Hemmelgarn, B., Suissa, S., Huang, A., Boivin, J. F. & Pinard, G. Benzodiazepine use and the risk of motor vehicle crash in the elderly. *JAMA*, 1997, 278: 27-31.
- Howard, M. E., Jackson, M. L., Kennedy, G. A., Swann, P., Barnes, M. & Pierce, R. J. The interactive effects of extended wakefulness and low-dose alcohol on simulated driving and vigilance. *Sleep*, 2007, 30: 1334-1340.
- Leufkens, T. R. M., Lund, J. S. & Vermeeren, A. Highway driving performance and cognitive functioning the morning after bedtime and middle-of-the-night use of gaboxadol, zopiclone and zolpidem. *J Sleep Res*, in press.
- Leufkens, T. R. M., Ramaekers, J. G., De Weerd, A. W., Riedel, W. J. & Vermeeren, A. On-the-road driving performance and driving related skills in untreated insomnia patients and chronic users of hypnotics. in prep.
- Leufkens, T. R. M. & Vermeeren, A. Highway driving in elderly the morning after bedtime use of hypnotics: a comparison between temazepam 20 mg, zopiclone 7.5 mg and placebo. *J Clin Psychopharmacol*, in press.
- Lim, J. & Dinges, D. F. Sleep deprivation and vigilant attention. *Ann N Y Acad Sc*, 2008, 1129: 305-322.
- Louwerens, J. W., Gloerich, A. B. M., Vries, D., G., Brookhuis, K. A. & O'Hanlon, J. F. The relationship between drivers' blood alcohol concentration (BAC) and actual driving performance during high speed travel. *Alcohol Drugs Traff Safe*, 1987, T86: 183-186.
- Mulder-Hajonides Van Der Meulen, W. R. E. H. *Measurement of subjective sleep quality*, Amsterdam, Elsevier, 1981.
- Neutel, I. Benzodiazepine-related traffic accidents in young and elderly drivers. *Hum Psychopharmacol Clin Exp*, 1998, 13: S115-S123.

- O'Hanlon, J. F. Driving performance under the influence of drugs: rationale for, and application of, a new test. *Br J Clin Pharmacol*, 1984, 18 Suppl 1: 121s-129s.
- Rey, A. *L'examen clinique en psychologie.*, Paris, Presses Universitaires de France, 1964.
- Smets, E. M., Garssen, B., Bonke, B. & De Haes, J. C. The Multidimensional Fatigue Inventory (MFI) psychometric qualities of an instrument to assess fatigue. *J Psychosom Res*, 1995, 39: 315-325.
- Spielberger, C. D., Gorsuch, R. L., Lushene, R. E., Vagg, P. R. & Jacobs, A. G. *Manual for the State-Trait Anxiety Inventory (Form Y)*, Palo Alto, Consulting Psychologists Press, Inc., 1983.
- Van Diest, R., Milius, H., Markusse, R. & Snel, J. The Sleep-Wake Experience List. *Tijds Soc Gezondheidsz*, 1989, 67: 343-347.
- Vermeeren, A. Residual effects of hypnotics: epidemiology and clinical implications. *CNS Drugs*, 2004, 18: 297-328.
- Vermeeren, A., Danjou, P. E. & O'Hanlon, J. F. Residual effects of evening and middle-of-the-night administration of zaleplon 10 and 20 mg on memory and actual driving performance. *Hum Psychopharmacol*, 1998, 13: S98-S107.
- Vermeeren, A., O'Hanlon, J. F., Declerck, A. C., & Kho, L Acute effects of zolpidem and flunitrazepam on sleep, memory and driving performance, compared to those of partial sleep deprivation and placebo. *Acta Ther*, 1995, 21: 47-64.
- Vermeeren, A., Riedel, W. J., Van Boxtel, M. P., Darwish, M., Paty, I. & Patat, A. Differential residual effects of zaleplon and zopiclone on actual driving: a comparison with a low dose of alcohol. *Sleep*, 2002, 25: 224-231.
- Verster, J. C., Volkerts, E. R., Schreuder, A. H., Eijken, E. J., Van Heuckelum, J. H., Veldhuijzen, D. S., Verbaten, M. N., Paty, I., Darwish, M., Danjou, P. & Patat, A. Residual effects of middle-of-the-night administration of zaleplon and zolpidem on driving ability, memory functions, and

CHAPTER 5

psychomotor performance. *J Clin Psychopharmacol*, 2002, 22: 576-583.

Zijlstra, F. R. H. Efficiency in work behavior. A design approach for modern tools. Delft, Delft University of Technology, 1993.

CHAPTER 6

Cognitive, psychomotor and actual driving performance in healthy volunteers after immediate and extended release formulations of alprazolam 1 mg

Published as:

Leufkens TRM, Vermeeren A, Smink BE, Van Ruitenbeek P, Ramaekers JG. (2007). Cognitive, psychomotor and actual driving performance in healthy volunteers after immediate and extended release formulations of alprazolam 1 mg. *Psychopharmacology*, 191, 951-959.

ABSTRACT

Alprazolam extended-release (XR) is approved for the treatment of panic disorder. This sustained formulation is absorbed in a delayed manner and is therefore expected to produce fewer and less severe side effects than its immediate release equivalent (alprazolam IR). The effect of alprazolam XR on potentially dangerous daily activities, such as driving a car, is expected to be less as compared to alprazolam IR.

The present study was designed to compare the effects of alprazolam XR (1 mg) and alprazolam IR (1 mg) on actual driving ability and cognitive function.

Eighteen healthy volunteers (aged 20-45 years) participated in a double blind, placebo-controlled, three-way crossover study. At 4 hours post dose, subjects performed a standardized driving test on a primary highway in normal traffic. Cognitive and psychomotor tests were assessed 1, 2.5 and 5.5 hours post dose. Memory functioning was measured only 1 hour after administration.

Both formulations severely impaired driving performance between 4 and 5 hours after administration. The magnitude of impairment in the driving test observed with alprazolam XR was about half that observed with alprazolam IR. Laboratory test results were in line with the driving data.

The acute impairing effects of alprazolam XR 1 mg on driving and psychomotor functions were generally less as compared to its immediate release equivalent, but still of sufficient magnitude to increase the risk of becoming involved in traffic accidents.

INTRODUCTION

Daytime sedation and impairment of psychomotor and cognitive functioning is one of the main problems associated with the use of benzodiazepine anxiolytics. This poses a crucial problem for users of these drugs who must operate vehicles. Epidemiological studies have shown that use of benzodiazepines is associated with an increased risk of car accidents (Barbone et al., 1998, Neutel, 1995, Neutel, 1998). Experimental studies have shown,

however, that effects on driving performance vary depending on the drug, dose and the formulation used (cf. Vermeeren, 2004).

Alprazolam is the most frequently used benzodiazepine in the treatment of panic disorder and anxiety (Isbister et al., 2004, RxList, 2005, Moroz, 2004, Verster et al., 2002). It is a 1,4 triazolobenzodiazepine and available in two formulations, an immediate release (IR) formulation and an extended release (XR) formulation. Alprazolam IR is rapidly absorbed and has a relatively short elimination half-life ranging between 10 and 18 hours (Greenblatt and Wright, 1993, Moroz, 2004). Following oral administration of alprazolam IR 1 mg peak plasma concentrations ranging from 12 to 22 µg/L are reached within 0.7 to 1.8 hours after intake (Greenblatt and Wright, 1993). Alprazolam IR is mainly prescribed in units of 0.25, 0.50 or 1.00 mg three times daily for patients suffering from anxiety, but daily doses can be raised to 10 mg for patients suffering from panic disorder (Busto et al., 2000).

Patients using alprazolam IR report benzodiazepine-related adverse events, such as drowsiness, dizziness and reduced alertness (Verster and Volkerts, 2004b). A vast amount of studies have shown that alprazolam IR in doses of 0.5 mg and higher impairs a variety of cognitive and psychomotor skills, such as memory, speed of responses and tracking performance (Bertz et al., 1997, Ellinwood et al., 1985, Greenblatt et al., 1988, Kroboth et al., 1998, Rickels, 2004, Scavone et al., 1992, Smith et al., 1984, Subhan et al., 1986, Vermeeren et al., 1995, Verster et al., 2002).

Alprazolam XR was developed in order to reduce the adverse events associated with alprazolam IR. It produces peak plasma concentrations that are about 50% of a similar dose of the IR formulation, and occur between 5 and 12 hours after administration (Busto et al., 2000, Eller and Della-Coletta, 1990, Fleishaker et al., 1989, Glue et al., 2006). Alprazolam XR produced fewer and less severe side effects than its IR equivalent. Moreover, it has been shown that cognitive and psychomotor performance is less impaired after alprazolam XR than after alprazolam IR (Busto et al., 2000, Mumford et al., 1995, Rickels, 2004).

It is unclear, however, if a reduction in performance impairment observed in laboratory tests of psychomotor function and cognition after alprazolam XR will have any implications for drivers who are being treated with alprazolam. In general, the validity of short psychomotor tests for predicting actual driving performance is limited. At best, drug induced impairments in psychomotor tests are only moderately correlated to drug induced impairment in driving performance as assessed in on-the-road driving tests. Consequently, it is widely accepted in the drug and driving community that experimental studies for establishing the driving hazard of a medicinal drug should proceed from conventional psychomotor tests to driving simulators and actual driving tests. Therefore, the final conclusions concerning a drug's impairing effect on driving should be based on combined results from these studies (ICADTS, 1999).

The present study was designed to establish the effects of alprazolam XR on actual driving performance as assessed in a standard on-the-road driving test (O'Hanlon, 1984). This test has been used repeatedly for assessing medicinal drug effects on actual driving in a large number of studies (reviews: Ramaekers, 2003, Vermeeren, 2004). Recently, it was applied in a study to assess the effect of a single dose of alprazolam IR 1 mg and placebo on actual driving performance in twenty healthy young volunteers (Verster et al., 2002). That study showed that alprazolam IR produced severe impairment of road tracking control, equivalent to the effect produced by a blood alcohol concentration of 1.5 g/L.

The primary purpose of the current study was to compare the effects of alprazolam XR with those of alprazolam IR on performance of healthy subjects in a standardized highway driving test. It was expected that driving impairment would be less after alprazolam XR as compared with alprazolam IR, due to differences in the pharmacokinetic profiles of both formulations. The secondary purpose was to compare the effects on cognitive and psychomotor functioning related to driving in a controlled laboratory setting.

METHODS AND MATERIALS

Subjects

Eighteen healthy volunteers (9 men and 9 women) were recruited by means of advertisements in local newspapers and public buildings. Their mean \pm SE age was 32.3 ± 2.0 years. Volunteers were screened by a telephone interview, health questionnaire and medical examination. The medical examination included blood hematology and chemistry, urinalysis, drug and pregnancy screening, and a 12-lead electrocardiogram. Inclusion criteria were age between 21 and 45 years, good physical and mental health, body mass index between 18 and 28 kg/m^2 , possession of a driving license for more than 3 years and average driving experience of at least 5000 km/year. Volunteers with any cardiovascular, endocrine, psychiatric and/or neurological condition were excluded, as were subjects with a history of drug abuse or currently using psychoactive medication, hypotension ($< 90/50 \text{ mmHg}$), liver disorder, pregnancy or lactation, and drinking more than 20 alcoholic consumptions per week.

From one week before participation in the study until completion of the last treatment period, subjects were not allowed to use any prescribed medicines or drugs of abuse. During the study period it was not allowed to participate in any other biomedical research. Subjects had to refrain from alcohol and caffeine 24 hours before testing. On test days, subjects were not allowed to consume any food 3 hours prior to arrival. During testing smoking was prohibited.

The study's approval was obtained from the medical ethics committee of Maastricht University. The study was conducted according to the code of ethics on human experimentation established by the World Medical Association's Declaration of Helsinki (1964) and amended in Edinburgh (2000). After complete description of the study to the subjects, written informed consent was obtained.

Design and treatment

The study was conducted according to a double-blind, placebo-controlled, 3-way crossover design. Treatments were single oral doses of alprazolam 1 mg immediate release (IR), alprazolam 1 mg extended release (XR), and placebo. Study medication was supplied in three capsules (double dummy) at 9 a.m. of each test day. Treatment orders were balanced by randomly assigning six treatment orders to 18 subjects. The minimum period between successive treatments was 7 days.

Testing procedure

Before the first treatment period all subjects received a comprehensive training of the driving and laboratory tasks. The standardized highway driving test was undertaken between 4 and 5 hours after dosing, i.e. the time plasma concentrations of the XR formulation were expected to be at a maximum. The Stop Signal Task and a Divided Attention Task were performed at 1, 2.5 and 5.5 hours after dosing. A Word Learning Task was performed at 1 hour post dose. Subjects consumed two standardized light meals 0.5 hours before and 3.5 hours after drug intake.

Driving and laboratory tasks

In the one hour driving test (O'Hanlon, 1984) subjects operate a specially instrumented vehicle over a 100 km (61 mi) primary highway circuit while maintaining a constant speed of 95 km/h (58 mi/h) and a steady lateral position between the delineated boundaries of the right (slower) traffic lane. Subjects are accompanied by a licensed driving instructor with access to dual controls. During the test, the car's speed and lateral position with respect to left lane-line are continuously recorded. These signals are edited off-line to yield the Standard Deviation of Lateral Position (SDLP in centimeters) which is taken as the primary outcome variable. SDLP is a measure of road tracking error or 'weaving'. SDLP has proven to be sensitive to the sedative and stimulating effects of various psychoactive drugs such as anxiolytics (O'Hanlon et al., 1995, Verster, 2005), hypnotics (Vermeeren, 2004), antidepressants (Ramaekers,

2003) and antihistamines (O'Hanlon and Ramaekers, 1995, Verster and Volkerts, 2004a).

The Divided Attention Task measures the ability to perform two tasks simultaneously during 12 minutes (Moskowitz, 1973). The primary subtask is a compensatory tracking task set at a constant level of difficulty. The secondary subtask is a visual search task in which the subject has to monitor 24 asynchronously changing single digits presented in the four corners of a screen. The subjects are instructed to remove their foot from a pedal as rapidly as possible whenever they detect the digit '2'. The main performance parameters are average tracking error (in mm) and number of control losses in the tracking task and number of misses and speed of target detection (in ms) in the visual search task. These parameters are transformed to standard (z) scores for each task. Performance in this test has proven sensitive to the effects of many sedative drugs such as doses of alcohol, antidepressants, antipsychotics, antihistamines and the residual effects of hypnotics (Ramaekers et al., 1999, Robbe and O'Hanlon, 1995, Vermeeren et al., 2002, Vuurman et al., 1994).

The Stop Signal Task assesses inhibitory control, defined as the ability to stop a pending thought or action (Logan, 1994). The paradigm consists of two concurrent tasks, i.e. a stop and a go task. The current test was adapted from an earlier version by Fillmore, Rush and Hays (Fillmore et al., 2002) and has been validated for showing stimulant and sedative drug effects (Ramaekers 2005; 2006). The go signals are four letters (A, B, C or D) presented one at a time in the center of a computer screen. Subjects are required to respond to each letter as quickly as possible by pressing one of two response buttons by either the left (A or C) or right (B or D) index finger. In the stop task, subjects are required to withhold any response in case a stop signal (a visual cue appearing in one of the four corners of the screen) is presented. Stop signals are presented 12 times at each of the four delays after the onset of a letter: 50, 150, 250, 350 msec. The dependent variables are reaction times to go signals (Go RT), the average delay needed to inhibit successfully the ongoing response (stop signal reaction time; SSRT) and the total number of false alarms.

The Word Learning Task assesses memory for verbal information (Rey, 1964). In this test, 15 monosyllabic nouns are sequentially presented on a computer screen for 2 sec and the subject is required to read the words aloud. At the end of the sequence, the subject is asked to recall as many words as possible, in any order. This procedure is repeated five times and the total number of correct recalls in five trials is referred to as the Immediate Recall Score (IRS). After a delay of at least 20 minutes the subject is again required to recall as many words as possible. During this trial, the nouns are not presented. The total number of correct recalls is referred to as the Delayed Recall Score (DRS). Finally, a sequence of 30 monosyllabic nouns is presented, containing 15 nouns from the original set and 15 new nouns in random order. The subject has to indicate whether a noun originates from the old or from the new set. The total number of correct indications is referred to as the Recognition Score (RS). The reaction time of decision is measured and is referred to as the Recognition Reaction Time (RRT). Performance in this test has previously been shown to be sensitive to the effects of alprazolam IR in doses of 0.5 and 1 mg (Vermeeren et al., 1995).

Serum concentrations

Alprazolam was determined by measuring serum concentrations. Blood samples were collected at 55 minutes and 6 hours after ingestion of the drug. Samples were centrifuged after a clotting period and serum was frozen at -20°C until analyses for pharmacokinetic assessments. Serum was analyzed for serum concentrations of alprazolam and its metabolite α -hydroxy-alprazolam using a Liquid Chromatography-Tandem Mass Spectrometry Method (LC-MS-MS) with Electrospray Interface (ESI).

Internal standards, d5-alprazolam and d5- α -hydroxy-alprazolam, were added to 1.0 mL serum sample before solid-phase extraction (OASIS HLB®, Waters, Etten-Leur, The Netherlands). The analytes were eluted from the cartridges with 1.5 mL acetonitrile, after washing with 2 mL water and 2 mL acetonitrile/water 10% v/v. The serum extracts were evaporated and reconstituted in 50 μ L acetonitrile/water 20% v/v before analysis.

The LC-MS system consisted of a TSP Spectra SYSTEM (Finnigan, Breda, The Netherlands), including a SN4000 controller, a vacuum degasser (SCM 1000), a pump (P4000) and an auto sampler (AS3000), connected to an ion trap mass spectrometer (LCQ, Finnigan). Chromatographic data were acquired and processed using X-calibur™ 1.2 software (Finnigan). The method used an Atlantis C18 column (150x2.1 mm, Waters, Etten-Leur, The Netherlands). Injection volume was 10 µL. The gradient used in this LC-MS(MS) method was acetonitrile/formic acid (0.005 M), 10% to 90% v/v acetonitrile. The time-course of the gradient was as follows: t=0-1 minutes (10-40% v/v acetonitrile), t=1-7 minutes (40 v/v % acetonitrile), t=7-8 minutes (40-90% v/v acetonitrile), t=8-9 minutes (90% v/v acetonitrile), t=9-10 minutes (90-10% v/v acetonitrile). Parent ions (m/z 309, 314, 325 and 330 for alprazolam, d5-alprazolam, α-hydroxy-alprazolam and d5-α-hydroxy-alprazolam, respectively) and product ions (m/z 274 and 281 for alprazolam, m/z 279 and 286 for d5-alprazolam, m/z 279, 297 and 307 for α-hydroxy-alprazolam and m/z 284, 302 and 312 for d5-α-hydroxy-alprazolam) were detected after collision.

The linear range for the assay was 1-10 ng/mL for alprazolam and 0.5-5 ng/mL for α-hydroxy-alprazolam. The limit of quantification (concentration with an intra-day standard deviation of 20%) was 1 ng/mL for alprazolam and 0.5-1 ng/ml for α-hydroxy-alprazolam. The accuracy was satisfactory (deviation from calibrated external control 10%). Inter-day precision was not determined, because in forensic case work, calibration curves are included in each analytical run.

Statistical analyses

Sample size was based on a power calculation for detecting a clinically relevant effect of 2.4 cm in the primary measure of this study, the Standard Deviation of Lateral Position (SDLP). This change corresponds to the effects of alcohol on SDLP while blood alcohol concentrations (BAC) are 0.5 g/L as measured in a previous study (Louwerens et al., 1987). Given that test-retest reliability of the driving test is at least $r = .70$, a group of 18 subjects should permit detection of

CHAPTER 6

a mean change in SDLP of 2.0 cm, with a power of at least 90% and an α risk of 0.05.

The global model used in the analysis of variance (ANOVA) of all cognitive and psychomotor parameters included *subject*, *period*, *treatment* and *time of testing*. In case of a significant overall effect of treatment, a subsequent analysis for comparing separate drug treatments was conducted using three simple contrasts.

All statistical analyses were done by using the SPSS statistical program (version 12.0.1 for Windows; SPSS Inc., Chicago, Ill.).

RESULTS

A summary of the cognitive, driving, and psychomotor tests is shown in Table 1.

Missing data

Word Recognition Test data were incomplete for 5 subjects and Stop Signal Task data were incomplete for 6 subjects due to technical problems. Only complete data sets entered the analysis.

ALPRAZOLAM EXTENDED AND IMMEDIATE RELEASE

Table 1. Summary of the results of the Road Tracking Test, Cognitive and Psychomotor Tests in healthy subjects in a crossover trial of alprazolam IR (1mg), alprazolam XR (1 mg) and placebo (n = 18)

					Simple contrast analysis		
					PLA	PLA	XR
					vs	vs	vs
					XR	IR	IR
Measure	Time	Mean (SE)					
		Placebo	Alprazolam XR	Alprazolam IR	p	p	p
Road Tracking Test							
SDLP (cm)	4.0	19.50 (.79)	23.44 (.44)	27.68 (1.40)	***	***	***
SDS (km/h)	4.0	2.18 (.19)	2.48 (.18)	3.01 (.34)	-	-	-
Divided Attention Test							
z-AE + z-ln(cl)	1.0	-.94 (.28)	-.21 (.34)	.71 (.46)	*	***	*
	2.5	-.74 (.33)	-.01 (.35)	1.08 (.40)	*	***	*
	5.5	-.73 (.32)	.43 (.34)	.40 (.46)	**	**	NS
z-RT + z-ln(mi)	1.0	-.96 (.33)	-.62 (.35)	.47 (.51)	NS	**	*
	2.5	-.55 (.32)	.21 (.40)	1.30 (.54)	*	**	*
	5.5	-.69 (.37)	.19 (.37)	.66 (.53)	*	*	NS
Stop Signal Task							
Go RT (ms)	1.0	645 (36)	642 (28)	704 (52)	-	-	-
	2.5	640 (32)	645 (30)	716 (40)	NS	***	***
	5.5	622 (32)	620 (34)	670 (39)	-	-	-
Stop RT (ms)	1.0	284 (15)	279 (12)	391 (13)	NS	***	***
	2.5	268 (9)	285 (11)	343 (21)	NS	**	*
	5.5	263 (9)	277 (9)	302 (19)	NS	*	NS
FA	1.0	8.92 (2.78)	9.00 (3.00)	8.17 (2.63)	-	-	-
	2.5	6.58 (2.41)	8.17 (2.51)	7.08 (1.96)	-	-	-
	5.5	5.58 (1.53)	7.33 (2.13)	7.42 (2.18)	-	-	-
Word Learning Test							
IRS	1.0	57.6 (1.11)	54.9 (1.64)	50.7 (1.83)	NS	***	NS
DRS	1.0	11.9 (.58)	11.2 (.55)	9.7 (.84)	NS	**	*
RS	1.0	28.7 (.49)	27.9 (.80)	28.3 (.52)	-	-	-
RRT (ms)	1.0	784 (21)	800 (24)	883 (49)	-	-	-

Abbreviations: PLA = placebo; IR = alprazolam Immediate Release; XR = alprazolam Extended Release; NS = not significant; SDLP = standard deviation of lateral position; SDS = standard deviation of speed; IRS = immediate recall score; DRS = delayed recall score; RS = recognition score; RRT = recognition reaction time; FA = false alarms; z-AE = z-score of average tracking error; z-ln(cl) = z-score of log transformed total number of control losses; z-RT = z-score of reaction time; z-ln(mi) = z-score of log transformed total number of misses.

* p < 0.05; ** p < 0.01; *** p < 0.001

Road Tracking Test

Ten driving tests (18.5% out of 54 comprising the complete data set) were terminated prematurely because the driving instructors judged the subject to be too drowsy to continue safely. They terminated seven rides (38.9% out of 18 comprising one condition) in the IR-condition, and three rides (16.7%) in the XR-condition. The SDLP scores were calculated from the data collected until termination of each ride.

There was a significant treatment effect ($F_{2,16}=31.89$, $p<0.001$). Contrast analysis revealed that both drug formulations significantly increased SDLP (IR: $F_{1,17}=67.44$, $p<0.001$; XR: $F_{1,17}=36.86$, $p<0.001$). However, mean SDLP after alprazolam XR was significantly lower as compared to alprazolam IR ($F_{1,17}=34.37$, $p<0.001$). Figure 1 shows that SDLP increased with approximately 8 cm in the IR-condition and 4 cm in the XR-condition, as compared to placebo.

No overall differences between placebo and drug were found on mean speed and speed variability.

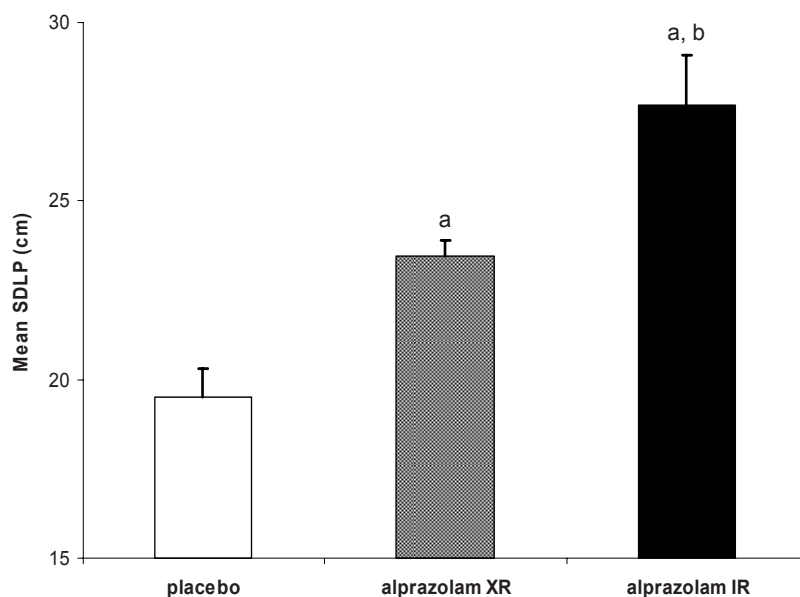


Figure 1. Mean (\pm SE) Standard Deviation of Lateral Position (SDLP) in each drug condition.

^a significantly different from placebo ($p < 0.001$) and ^b significantly different from alprazolam XR ($p < 0.001$)

Divided Attention Task

The distributions of control losses and misses were highly skewed. Therefore, they were transformed to their natural log (ln) scores before transformation to z-scores. ANOVA of the sum score of the z-scores of the average error and natural log of the total number of control losses revealed a significant overall treatment effect ($F_{2,16}=11.74$, $p<0.001$). Effects of treatments were further analyzed at separate times after drug intake. These analyses showed that tracking performance was significantly impaired at 1, 2.5 and 5.5 hours after administration of alprazolam IR 1mg (1 hr: $F_{1,17}=15.88$, $p<0.001$; 2.5 hrs: $F_{1,17}=15.14$, $p<0.001$; 5.5 hrs: $F_{1,17}=12.40$, $p<0.01$) and alprazolam XR 1 mg (1 hr: $F_{1,17}=6.31$, $p<0.05$; 2.5 hrs $F_{1,17}=7.00$, $p<0.05$; 5.5 hrs: $F_{1,17}=12.26$, $p<0.01$). The effects of the XR formulation were less severe, however, than those of the IR formulation at 1 hour ($F_{1,17}=15.42$, $p<0.05$ and 2.5 hours post dose ($F_{1,17}=21.32$, $p<0.05$), but no longer at 5.5 hours post dose.

A significant overall treatment effect in target detection performance, as measured by the sum of the z-scores of the reaction time and natural log of total number of misses was found ($F_{2,16}=5.72$, $p<0.05$). Analyses at separate times after administration revealed a significant impairment on target detection by alprazolam IR compared to placebo at all times of measurement ($F_{1,17}=6.89$, $p<0.05$). Alprazolam XR did not differ significantly from placebo 1 hour post dose. On 2.5 and 5.5 hours post dose target detection differed significantly between placebo and alprazolam XR (respectively, $F_{1,17}=4.46$, $p<0.05$; $F_{1,17}=6.49$, $p<0.05$). Comparisons between both treatment conditions revealed significant differences at 1 hour and 2.5 hours post dose (respectively, $F_{1,17}=5.84$, $p<0.05$; $F_{1,17}=6.72$, $p<0.05$). At 5.5 hours after ingestion target detection was not significantly different between both treatment conditions.

Stop Signal Task

Analysis revealed a significant overall treatment effect on the go reaction time ($F_{2,10}=6.20$, $p<0.05$). Separate analyses for each time of testing revealed significant differences between treatments at 2.5 hours post dose. At that time, relative to placebo, the go reaction time was significantly longer after

alprazolam IR ($F_{1,11}=22.87$, $p<0.001$), but not after alprazolam XR. Moreover, the increment in reaction time after alprazolam IR was also significantly different from that after alprazolam XR ($F_{1,11}=23.70$, $p<0.001$). No interaction was found between treatment and time of measurement.

A significant interaction effect between treatment and time of measurement in stop signal reaction time (SSRT) was found ($F_{2,10}=58.94$, $p<0.001$). Placebo drug comparisons for each time of testing showed that alprazolam IR increased SSRT significantly at each time of testing ($F_{1,11}=6.01$, $p<0.05$) whereas alprazolam XR did not. SSRT after alprazolam XR was significantly better than after alprazolam IR 1 hour and 2.5 hours after ingestion ($F_{1,11}=109.92$, $p<0.001$; $F_{1,11}=6.44$, $p<0.05$, respectively), but no longer at 5.5 hours post dose.

For the total number of false alarms data, analyses revealed no significant effects.

Word Learning Test

Analysis of the total number of words correctly recalled over five memory trials, as reflected by the immediate recall score, showed a significant overall treatment effect ($F_{2,16}=9.08$, $p<0.01$). Placebo-drug comparisons revealed a significant impairing effect of alprazolam IR at 1 hour after administration, but not of alprazolam XR. No significant difference was found between alprazolam IR and alprazolam XR.

The delayed recall score also revealed a significant overall treatment effect. As Delayed recall in the alprazolam IR condition was significantly lower than in the placebo condition ($F_{1,17}=10.22$, $p<0.01$). Delayed recall after alprazolam XR ingestion did not significantly differ from placebo. The difference between alprazolam IR and alprazolam XR was significant ($F_{1,17}=4.64$, $p<0.05$).

No significant effects were found on performance in the recognition test.

Serum concentrations

Mean (SE) serum concentrations for alprazolam at 55 minutes post dose were 4.9 (1.0) $\mu\text{g/L}$ after alprazolam IR administration and 1.7 (0.2) $\mu\text{g/L}$ after alprazolam XR administration. After approximately 6 hours of drug ingestion

mean (SE) serum concentrations for alprazolam were 10.6 (0.5) µg/L after alprazolam IR and 9.0 (0.6) µg/L after alprazolam XR. The alprazolam metabolite α-hydroxy-alprazolam was not detectable in the serum. The metabolite is expected to be present in plasma in unconjugated form at less than 10% of the alprazolam level (Smith and Kroboth 1987).

DISCUSSION

Results from the present study show that both alprazolam 1 mg formulations administered as single doses to healthy nonanxious volunteers significantly impair performance on the standardized highway driving test. The IR formulation produced a mean increase in SDLP of 8.2 cm and the XR formulation produced an increase of 3.9 cm. Although the magnitude of effect on SDLP was reduced by about 50% after alprazolam XR, the impairment was still severe. The acute effects of alprazolam IR and alprazolam XR would be the equivalents of driving with a BAC above the legal limit for alcohol in most industrialized countries, i.e. 0.5 g/L (Louwerens et al., 1987). BACs of above 0.5 g/L have been shown to progressively increase the risk of becoming involved in a serious traffic accident by a factor of 2 or more (Borkenstein et al., 1974). The number of driving tests that were prematurely terminated supported the SDLP data. Under the alprazolam XR condition three (16.7%) subjects were not able to complete the driving test. Alprazolam IR caused an early ending of the test in seven (38.9%) subjects. The most frequent reason for aborting the test prematurely was excessive sleepiness.

The detrimental effect of alprazolam IR on driving in the present study is similar to that found in a previous study employing the same standardized highway driving test. In that study, Verster et al. (2002) found a mean increment in SDLP of approximately 9 cm between 1-2 hours following a single dose of alprazolam IR 1 mg. This indicates that sensitivity of the subjects in the present study to the effects of alprazolam was normal.

Although the laboratory tests are not expected to strongly predict driving performance, they usually provide some insight as to what extent driving is

affected after drug intake. Driving ability is not one distinct skill, but a combination of a series of mental and behavioral functions (Vermeeren and De Gier, 1995). Therefore, performance in laboratory tests assessing different aspects of driving can provide insight into what aspects of driving behavior are most sensitive to the effects of a particular drug, although performance in any single test is not highly correlated to driving performance itself. As expected, alprazolam IR significantly impaired performance on all tasks as compared with placebo. It impaired tracking and peripheral visual search in the divided attention task, response speed and inhibitory control in the stop signal task and immediate and delayed recall in the word learning task. In contrast, alprazolam XR only impaired performance in the divided attention task, but not in the stop signal and memory tests, indicating a reduction in adverse effects.

This reduction of impairing effects was most pronounced within the first 4 hours after administration of both formulations, when blood levels of alprazolam XR were still rising and those of alprazolam IR were at their peak, as shown by the serum concentrations. Within this time period, the effects of alprazolam XR were significantly less severe in the majority of the tests, as compared with those of alprazolam IR. At 5.5 hours post dosing performance effects and serum concentrations became comparable. At this point in time, alprazolam XR achieves peak plasma concentrations, whereas alprazolam IR plasma levels are already descending. Thus, peak effects of alprazolam XR are less severe than those of alprazolam IR.

A potential limitation of the present study might be that the effects were assessed only after a single dose administration of study treatments. Alprazolam-induced impairment may become less severe after chronic administration of alprazolam, as it is well known that tolerance to the sedating effects of benzodiazepines can develop after repeated use (Curran, 1986). However, it has also been shown that tolerance to the impairing effects of benzodiazepines is never complete. An epidemiological study by Neutel (1995) demonstrated that benzodiazepines increase the relative risk of becoming involved in traffic accidents during the first week of treatment and that this risk remains, albeit to a lesser extent with passage of time. During the first week of

treatment, the benzodiazepine users' relative risk was 13.5. After one month the relative risk had declined to 2.6. The implication thus seems to be that benzodiazepine impairment persists over time, but to a lesser degree as observed after initial dosing. A similar pattern was found in an experimental study assessing the effects on driving performance of diazepam 5 mg treatment during 4 consecutive weeks in 12 patients with generalized anxiety disorder (van Laar et al., 1992). Diazepam significantly impaired driving performance, as reflected by an elevated SDLP, in the first three weeks of treatment. Therefore, it was concluded that driving performance of patients will be affected at least during early, chronic treatment.

It might be argued that performance of healthy subjects may be different from performance of patients suffering from anxiety or panic disorder. Moreover, as healthy volunteers do not have a history of benzodiazepine use, the effect of alprazolam may be stronger than that in patients who have already been using alprazolam for an extended period of time. Yet, these notions have never been confirmed in scientific research. On the contrary, O'Hanlon and associates (O'Hanlon et al., 1995) have shown that driving performance after both single and repeated doses of benzodiazepine anxiolytics did not differ in healthy volunteers and patients. Moreover, these authors showed that baseline and placebo performances were comparable between both groups. This implies that healthy volunteer models can be used for predicting drug effects on driving in patient populations. Therefore, if the effects of both formulations of alprazolam observed in the present study also apply to anxious individuals receiving the medications as clinical treatment, the risk of becoming involved in a car accident may be increased.

In conclusion, the impairing effects of alprazolam XR 1 mg on driving and cognition were generally less as compared to its immediate release equivalent, but still of sufficient magnitude to increase the risk of becoming involved in traffic accidents.

REFERENCES

- Barbone, F., McMahon, A. D., Davey, P. G., Morris, A.D., Reid, I. C., McDevitt, D.G. & MacDonald, T. M. Association of road-traffic accidents with benzodiazepine use. *Lancet*, 1998, 352: 1331-1336.
- Bertz, R. J., Kroboth, P. D., Kroboth, F. J., Reynolds, I. J., Salek, F., Wright, C. E. & Smith, R. B. Alprazolam in young and elderly men: sensitivity and tolerance to psychomotor, sedative and memory effects. *J Pharmacol Exp Therap*, 1997, 281: 1317-1329.
- Borkenstein, R. F., Crowther, F. R., Shumate, R. P., Ziel, W. B. & Zylman, R. The role of drinking driver in traffic accidents: the Grand Rapids Study. *Blutalkohol*, 1974, 11: 1-131.
- Busto, U. E., Kaplan, H. L., Wright, C. E., Gomez Mancilla, B., Zawertailo, L., Greenblatt, D. J. & Sellers, E. M. A comparative pharmacokinetic and dynamic evaluation of alprazolam sustained-release, bromazepam, and lorazepam. *J Clin Psychopharmacol*, 2000, 20: 628-635.
- Curran, H. V. Tranquillising memories: a review of the effects of benzodiazepines on human memory. *Biol Psychol*, 1986, 23: 179-213.
- Eller, M. G. & Della-Coletta, A. A. Absence of effect of food on alprazolam absorption from sustained release tablets. *Biopharm Drug Dispos*, 1990, 11: 31-37.
- Ellinwood, E. H., Jr., Heatherly, D. G., Nikaido, A. M., Bjornsson, T. D. & Kilts, C. Comparative pharmacokinetics and pharmacodynamics of lorazepam, alprazolam and diazepam. *Psychopharmacol*, 1985, 86: 392-399.
- Fillmore, M. T., Rush, C. R. & Hays, L. Acute effects of oral cocaine on inhibitory control of behavior in humans. *Drug Alcohol Depend*, 2002, 67: 157-167.
- Fleishaker, J. C., Phillips, J. P., Eller, M. G. & Smith, R. B. Pharmacokinetics and pharmacodynamics of alprazolam following single and multiple oral doses of a sustained-release formulation. *J Clin Pharmacol*, 1989, 29: 543-549.

- Glue, P., Fang, A., Gandelman, K. & Klee, B. Pharmacokinetics of an extended release formulation of alprazolam (Xanax XR) in healthy normal adolescent and adult volunteers. *Am J Ther*, 2006, 13: 418-422.
- Greenblatt, D. J., Harmatz, J. S., Dorsey, C. & Shader, R. I. Comparative single-dose kinetics and dynamics of lorazepam, alprazolam, prazepam, and placebo. *Clin Pharmacol Ther*, 1988, 44: 326-334.
- Greenblatt, D. J. & Wright, C. E. Clinical pharmacokinetics of alprazolam. Therapeutic implications. *Clin Pharmacokinet*, 1993, 24: 453-471.
- ICADTS. Guidelines on experimental studies undertaken to determine a medicinal drug's effect on driving or skills related to driving. Cologne, Bundes Anstalt fuer Strassenwesen (BASt), 1999.
- Isbister, G. K., O'Regan, L., Sibbritt, D. & Whyte, I. M. Alprazolam is relatively more toxic than other benzodiazepines in overdose. *Br J Clin Pharmacol*, 2004, 58: 88-95.
- Kroboth, P. D., Folan, M. M., Bauer, K. S., Tullock, W., Wright, C. E. & Sweeney, J. A. Do alprazolam-induced changes in saccadic eye movement and psychomotor function follow the same time course? *J Clin Pharmacol*, 1998 38: 337-346.
- Logan, G. D. On the ability to inhibit thought and action: A users' guide to the Stop Signal Paradigm Inhibitory processes in attention, memory, and language, 1994, pp 189-239.
- Louwerens, J. W., Gloerich, A. B. M., de Vries, G., Brookhuis, K. A. & O'Hanlon, J. F. The relationship between drivers' blood alcohol concentration (BAC) and actual driving performance during high speed travel. *Alcohol Drug Traff Safe*, 1987, T86: 183-186.
- Moroz, G. High-potency benzodiazepines: recent clinical results. *J Clin Psychiat*, 2004, 65 Suppl 5: 13-18.
- Moskowitz, H. Laboratory studies of the effects of alcohol on some variables related to driving. *J Saf Res*, 1973, 5: 185-199.
- Mumford, G. K., Evans, S. M., Fleishaker, J. C., Griffiths, R. R. Alprazolam absorption kinetics affects abuse liability. *Clin Pharmacol Ther*, 1995, 57: 356-365.

CHAPTER 6

- Neutel, C. I. Risk of traffic accident injury after a prescription for a benzodiazepine. *Ann Epidemiol*, 1995, 5: 239-244.
- Neutel, I. Benzodiazepine-related traffic accidents in young and elderly drivers. *Hum Psychopharmacol Clin Exp*, 1998, 13: S115-S123.
- O'Hanlon, J. F. Driving performance under the influence of drugs: rationale for, and application of, a new test. *Br J Clin Pharmacol*, 1984, 18 Suppl 1: 121s-129s.
- O'Hanlon, J. F. & Ramaekers, J. G. Antihistamine effects on actual driving performance in a standard test: a summary of Dutch experience, 1989-94. *Allergy*, 1995, 50: 234-242.
- O'Hanlon, J. F., Vermeeren, A., Uiterwijk, M. M., van Veggel, L. M. & Swijman, H. F. Anxiolytics' effects on the actual driving performance of patients and healthy volunteers in a standardized test. An integration of three studies. *Neuropsychobiol*, 1995 31: 81-88.
- Ramaekers, J. G. Antidepressants and driver impairment: empirical evidence from a standard on-the-road test. *J Clin Psychiat*, 2003, 64: 20-29.
- Ramaekers, J. G. & Kuypers, K. P. C. Acute effects of 3,4-methylenedioxymethamphetamine (MDMA) on behavioral measures of impulsivity: Alone and in combination with alcohol. *Neuropsychopharmacol*, 2006, 31: 1048-1055.
- Ramaekers, J.G., Louwerens, J. W., Muntjewerff, N. D., Milius, H., De Bie, A. & Rosenzweig, P. Psychomotor, cognitive, extrapyramidal, and affective functions of healthy volunteers during treatment with an atypical (amisulpride) and a classic (haloperidol) antipsychotic. *J Clin Psychopharmacol*, 1999, 19: 209-221.
- Rey, A. L'examen clinique en psychologie. Presses Universitaires de France, Presses Universitaires de France, 1964.
- Rickels, K. Alprazolam extended-release in panic disorder. *Expert Opin Pharmacother*, 2004, 5: 1599-1611.
- Robbe, H. W. & O'Hanlon, J. F. Acute and subchronic effects of paroxetine 20 and 40 mg on actual driving, psychomotor performance and subjective

- assessments in healthy volunteers. *Eur Neuropsychopharmacol*, 1995, 5: 35-42.
- RxList. Top 200 prescriptions for 2005 by number of US prescriptions dispensed. 2005, <http://rxlist.com/top200.htm>.
- Scavone, J. M., Greenblatt, D. J., Goddard, J. E., Friedman, H., Harmatz, J. S. & Shader, R. I. The pharmacokinetics and pharmacodynamics of sublingual and oral alprazolam in the post-prandial state. *Eur J Clin Pharmacol*, 1992, 42: 439-443.
- Smith, R. B. & Kroboth, P. D. Influence of dosing regime on alprazolam and metabolite serum concentrations and tolerance to sedative and psychomotor effects. *Psychopharmacol*, 1987, 93: 105-112.
- Smith, R. B., Kroboth, P. D., Vanderlugt, J. T., Phillips, J. P. & Juhl, R. P. Pharmacokinetics and pharmacodynamics of alprazolam after oral and IV administration. *Psychopharmacol*, 1984, 84: 452-456.
- Subhan, Z., Harrison, C. & Hindmarch, I. Alprazolam and lorazepam single and multiple-dose effects on psychomotor skills and sleep. *Eur J Clin Pharmacol*, 1986, 29: 709-712.
- van Laar, M. W., Volkerts E. R. & van Willigenburg, A. P. Therapeutic effects and effects on actual driving performance of chronically administered buspirone and diazepam in anxious outpatients. *J Clin Psychopharmacol*, 1992, 12: 86-95.
- Vermeeren, A. Residual effects of hypnotics: epidemiology and clinical implications. *CNS Drugs*, 2004, 18: 297-328.
- Vermeeren, A. & De Gier, J. J. Methodological guidelines for experimental research in Drugs and Driving: accomplishments and future needs. In Krueger, H.-P., Kohnen, R. & Schoch, H. (Eds.) *Medicamente in Strassenverkehr: Auftreten, Risiken Konsequenzen*. Stuttgart, Gustav Fisher Verlag, 1995.
- Vermeeren, A., Jackson, J. L., Muntjewerff, N. D., Quint, P. J., Harrison, E. M. & O'Hanlon, J.F. Comparison of acute alprazolam (0.25, 0.50 and 1.0 mg) effects versus those of lorazepam 2 mg and placebo on memory in

- healthy volunteers using laboratory and telephone tests. *Psychopharmacol*, 1995, 118: 1-9.
- Vermeeren, A., Riedel, W. J., van Boxtel, M. P., Darwish, M., Paty, I., Patat, A. Differential residual effects of zaleplon and zopiclone on actual driving: a comparison with a low dose of alcohol. *Sleep*, 2002, 25: 224-231.
- Verster, J. C., Veldhuijzen, D. S., & Volkerts, E. R. Is it safe to drive a car when treated with anxiolytics? Evidence from on-the-road driving studies during normal traffic. *Curr Psychiat Rev*, 2005, 1: 215-225.
- Verster, J. C. & Volkerts, E. R. Antihistamines and driving ability: evidence from on-the-road driving studies during normal traffic. *Ann Allergy Asthma Immunol*, 2004a, 92: 294-303.
- Verster, J. C. & Volkerts, E. R. Clinical pharmacology, clinical efficacy, and behavioral toxicity of alprazolam: a review of the literature. *CNS Drug Reviews*, 2004b, 10: 45-76.
- Verster, J. C., Volkerts, E. R. & Verbaten, M. N. Effects of alprazolam on driving ability, memory functioning and psychomotor performance: a randomized, placebo-controlled study. *Neuropsychopharmacol*, 2002, 27: 260-269.
- Vuurman, E., Uiterwijk, M. M., Rosenzweig, P. & O'Hanlon, J. F. Effects of mizolastine and clemastine on actual driving and psychomotor performance in healthy volunteers. *Eur J Clin Pharmacol*, 1994, 47: 253-259.

CHAPTER 7

General Discussion

Healthy, young volunteers versus elderly insomnia patients

A major question addressed in the dissertation was whether the results of studies investigating residual effects of hypnotics in healthy, young, medication naïve volunteers can be generalized to the target population, i.e. patients suffering from insomnia. As has been mentioned in the previous chapters, healthy, young, medication naïve volunteers differ from the typical insomnia patient in age, disorder and use of hypnotics.

Age

The first difference between young volunteers and insomnia patients is age. It has been shown that insomnia is most prevalent in middle-aged and elderly individuals (Drake et al., 2003, Kamel and Gammack, 2006). Age-related differences in pharmacokinetics and pharmacodynamics may result in prolonged effects of hypnotics in older patients (Woodward, 1999). As a result, it could be expected that the detrimental effects of hypnotics on driving performance in older patients are increased compared with younger individuals. Results presented in *chapters 2, 3 and 5* show that these expectations cannot be confirmed. *Chapters 2 and 5* demonstrate that the mean increase from placebo in SDLP after administration of zopiclone 7.5 mg was similar between healthy elderly drivers and healthy younger drivers. In addition, as was found earlier in a study with healthy younger volunteers (O'Hanlon and Volkerts, 1986), temazepam 20 mg appeared unlikely to produce residual effects on driving 10 hours or more after bedtime administration in healthy elderly aged 75 years or younger. Even more, it is shown in *chapter 3* that the effects of zopiclone 7.5 mg on driving performance in elderly, aged between 56 and 73 years, were generally less than those found in younger individuals. It may therefore be concluded that the residual effects of hypnotics are not prolonged or more severe in elderly drivers until the age of 75.

It can be argued that the absence of increased impairment of hypnotics on driving performance in elderly was due to the protective effects of driving experience. Epidemiological studies show that the risk of becoming involved in a traffic accident after use of hypnotics is lower in older drivers than in younger

less experienced drivers (Neutel, 1998). Yet, results in *chapter 3* could not reveal a strong relation between years of driving experience and magnitude of impaired driving performance. It was found that years of driving experience predicted only a small proportion of the variation of effects of hypnotics, implicating that the lack of increased residual effects of hypnotics in elderly cannot be explained by this factor. This finding may be explained by a common inclusion criterion of driving studies in general. One of the conditions for participation in driving studies is that subjects, both young and old, need to possess a valid driving license for at least three years. It has been shown that crash involvement risk decreases dramatically during the first few months after licensing (Sagberg and Bjornskau, 2006), suggesting that driving skills develop in a parallel fashion. The minimum of three years of driving experience is, therefore, expected to be sufficient to preclude major differences in fundamental driving skills.

Besides years of possession of a driving license, driving experience may also be expressed in average annual mileage. It may be assumed that elderly are less involved in car driving and they produce lower average annual mileages than younger drivers. Therefore, the inclusion study criterion of average annual mileage for older volunteers was at least 3000 km/year over the preceding three years, whereas it was 5000 km/year for younger drivers. If low annual mileage reduces driving performance then marked differences in driving experience as reflected by annual mileage would be reflected in elevated SDLP scores after placebo administration in elderly drivers as compared to younger. Results in *chapter 2* do not indicate that this is the case, however. SDLP scores in the placebo condition of the elderly were comparable to those found of younger drivers as presented in the study described in *chapter 1*. These results confirm previous conclusions that older individuals who drive 3000 km per year or more are safe drivers and do not differ from younger drivers (Alvarez and Fierro, 2008, Langford et al., 2006).

If baseline levels of driving performance are similar between older and younger drivers, the question rises why the elderly did not display the expected age-related increased sensitivity to the residual effects of hypnotics. As is

mentioned in *chapter 3*, the older subjects were younger than 75 years and were selected to be healthy subjects, because the aim of the study was to evaluate the effects in still active drivers. Pharmacokinetic and pharmacodynamic changes may be more likely to occur in individuals older than 75 years (Sgadari et al., 2000). Although there are people over the age of 75 who still participate in daily motorized traffic, we chose a more representative study sample of the elderly driving population.

Insomnia

The second difference between healthy, young, volunteers and insomnia patients is, for obvious reasons, the sleep disturbance. Patients may respond differently to the adverse effects of hypnotics than healthy young volunteers, because of the underlying disorder. It may be expected that efficacious hypnotics without residual effects improve daytime performance in insomniac patients, whereas healthy subjects do not benefit from the sleep-inducing effects of hypnotics. As a consequence, daytime performance in healthy subjects does not improve following a night with hypnotic administration.

It was, however, not clear whether driving performance as assessed by the standardized highway driving test would be affected by insomnia. Epidemiological studies have found that sleeping problems are associated with an increased risk of traffic accidents (Akerstedt et al., 2002, Sagberg, 2006), but experimental studies have not been able to unambiguously confirm these results (reviews: Fulda and Schulz, 2001, Riedel and Lichstein, 2000). A major methodological limitation in most experimental studies was that they used tests of short duration requiring low effort. Possible performance deficits in insomnia patients may have been masked by their ability to complete the tests with increased effort (Drummond et al., 2004). It was expected that the standardized highway driving test would circumvent these problems because of its prolonged attentional demands. Yet, results presented in *chapter 4* show that insomnia patients who had not used hypnotics in the night before the driving test did not drive worse than healthy, age-matched controls.

It could be argued that the absence of impairing effects on driving performance in insomnia patients may have been explained by the lack of objectively measured sleep complaints. According to polysomnographic recordings insomnia patients did not sleep less than healthy controls. As a consequence, differences in daytime performance are not expected to occur. Due to the fact that discrepancies between objective and subjective measures in sleep complaints have repeatedly been established (e.g. Carskadon et al., 1976, Orff et al., 2007, Vermeeren et al., 1995, Vignola et al., 2000), insomnia is now defined in the Diagnostic and Statistical Manual of Mental Disorder (DSM-IV) by subjective complaints lasting for at least 1 month of difficulty initiating and/or maintaining sleep or of nonrestorative sleep (APA, 1994). Its diagnosis is based on structured interviews, supplemented by a sleep diary providing information about subjective sleep quality and possible use of medication, alcohol, caffeine and nicotine (Espie, 2002). Polysomnographic recordings are no longer required for determination of insomnia, except when disorders such as sleep apnea are suspected. Analyses of the sleep diaries, which were kept by our insomnia patients for two weeks, revealed significant sleep disturbances. Therefore, according to current criteria the subject sample in the study described in *chapter 4* was a representative group of insomnia patients. This was additionally confirmed by their subjective estimates of sleep quality during the nights before performing the standardized highway driving test. Results showed that subjective evaluations of sleep by the patients were significantly worse than those by the self-defined good sleepers.

It is suggested nowadays that traditional sleep analyses have limited sensitivity to detect differences in sleep quality between insomnia patients and healthy, good sleepers (Bastien et al., 2003). Disturbances in sleep may not to be searched for in absolute parameters such as total sleep time or sleep onset latency, but in measures of high frequency EEG activity. In general, it is hypothesized that insomnia is a disorder characterized by central nervous system hyperarousal, which is reflected by elevated beta EEG activities (Bonnet and Arand, 1997). It has been shown repeatedly that beta EEG activity is increased in insomnia patients during non-REM sleep when compared to good

sleepers (cf. Perlis et al., 2001a). Since high frequency EEG activity in the beta range is associated with attention and perception in humans, this would suggest that insomnia patients have increased information and sensory processing during their sleep (Perlis et al., 2001b). In addition, evidence has been found that beta activity is negatively correlated with the perception of sleep quality (Perlis et al., 2001b), explaining subjective reports of disturbed sleep in insomnia patients.

Besides explaining subjectively disturbed sleep in insomnia patients, hyperarousal may also account for the lack of impairing effects found in the highway driving test. Arousal levels in insomnia patients appear not only to be elevated during the night, but also during the day (Bonnet and Arand, 1995). Insomnia patients may, therefore, be able to sustain their attention during a one hour driving test. Future research is needed to study arousal levels in both insomnia patients and healthy controls during car driving and laboratory tests assessing driving related skills.

It may also be inferred from the hyperarousal hypothesis that insomnia should not be mistaken for sleep deprivation. Healthy, good sleepers who are sleep deprived for a short period of time or even chronically, do not display the same symptomatology as insomnia patients do (Bonnet and Arand, 1996). For example, it has been shown that good sleepers who were experimentally submitted to a sleep pattern of subjective insomnia complaints for one week, i.e. frequent awakenings and arousals and a shortened total sleep time, did not resemble daily functioning of insomnia patients (Bonnet and Arand, 1996). Instead of elevated metabolic rates, the good sleepers' metabolism lowered. In addition, they did not report increased state measures of anxiety or depression as is typically found in insomnia patients. Even more, the usual long latency or inability to fall asleep during a multiple sleep latency test was not found in the good sleepers during the test week. On the contrary, latencies to fall asleep dropped significantly as the nights of insomnia increased.

Besides differences between sleep deprived good sleepers and insomnia patients in symptomatology, there are also differences in how daytime performance is affected. It has been shown that sleep deprivation has

significant impairing effects on a number of cognitive and psychomotor functions (cf. Pilcher and Huffcutt, 1996), whereas nearly no impaired performance has been found due to insomnia (Fulda and Schulz, 2001; *chapter 4*).

Chronic use of hypnotics

The third difference between healthy, young, medication naïve volunteers and the typical insomnia patient is the use of hypnotics. Although it is not recommended to use hypnotics for more than a period of 4 weeks, a large number of patients who are older than 65 years are treated for prolonged periods (Ashton, 2005, Paterniti et al., 2002). It has been shown, for example, that 60% of the British population of insomnia patients uses benzodiazepines for over 10 years (Curran et al., 2003). Frequent and chronic use of hypnotics may induce the development of tolerance to both the therapeutic and residual effects. Healthy good sleepers, on the other hand, do not use hypnotics and, thus, have not developed tolerance to the residual effects of hypnotics. Therefore, the effects found in healthy, medication naïve subjects may be an overestimation of the actual effects found in insomnia patients chronically using hypnotics.

Results presented in *chapter 5* indicate that the magnitude of effect of zopiclone 7.5 mg is significantly reduced in insomnia patients chronically using hypnotics as compared to healthy controls. These findings seem to confirm expectations of an overestimation of effect found in healthy volunteers. However, in *chapter 5* it was discussed that the insomnia patients who chronically used hypnotics may have experienced withdrawal symptoms during the placebo night. This was reflected by elevated SDLP scores in the placebo condition. Although the elevation did not reach statistical significance, the difference was +1.9 cm as compared to the healthy controls. This increased placebo score may have diminished the difference from zopiclone in the group of insomnia patients who chronically used hypnotics. Future studies are needed circumventing masking effects of withdrawal symptoms. For example, it may be possible to expand the placebo controlled, two-way crossover design as

described in *chapter 5* with an extra condition. In this condition a hypnotic should be administered which is known to be effective, but also known to be unlikely to produce residual effects on driving performance. SDLP scores in this condition are then expected to be lower than in the placebo condition, revealing withdrawal effects.

More insight about the development of tolerance to the residual effects of hypnotics on driving performance may be provided by studies using different experimental designs. For instance, it may be possible to include a group of insomnia patients starting with zopiclone 7.5 mg treatment in a study in which the residual effects on driving performance are investigated on fixed intervals during a prolonged period.

Besides information about the difference in the magnitude of effects of hypnotics between chronic users and healthy good sleepers, the study described in *chapter 5* has yielded other important information. Results show that insomnia patients initiating hypnotic use or changing in type of hypnotic can have impairing effects on driving performance. Even more, if insomnia patients use hypnotics intermittently on an 'as needed' base, tolerance may not develop. As a consequence, residual effects of hypnotics in this group of insomnia patients are significantly impairing driving performance. Therefore, patients starting or changing hypnotic treatment should be warned about the impairing effects of hypnotics on driving performance.

Gender

One of the objectives in the study presented in *chapter 3* was to determine whether there are significant differences between female and male volunteers in the severity of residual effects of zopiclone on driving performance. The majority of studies evaluating residual effects on driving performance comprises relatively small sample sizes and has not been able to compare performance between females and males. In the study described in *chapter 3* the raw data of four studies with comparable methodology were pooled in order to create a larger study sample. As a result, the effects of zopiclone 7.5 mg on driving performance were compared between 51 females and 50 males. Results

showed that there were no significant gender differences in the residual effects of zopiclone. Consequently, it was concluded that information about the impairing effects of zopiclone do not need to be specified for each gender separately.

Formulation

The final question presented in this dissertation was to what extent driving performance is impaired after administration of an extended release formulation of the frequently prescribed anxiolytic alprazolam. It was shown in experimental studies using laboratory tests that cognitive and psychomotor performance was less impaired after alprazolam extended release (XR) than after its immediate release equivalent (IR) (Busto et al., 2000, Mumford et al., 1995, Rickels, 2004). It was expected that results on the driving test would be in line with the results of the laboratory tests. However, as correlations between laboratory tests and the driving tests are, at best, moderate (ICADTS, 1999), the effects of alprazolam XR needed to be established with use of the standardized highway driving test.

Results showed that, although effects after administration of alprazolam XR 1 mg were halved as compared to those of alprazolam IR 1 mg, the extended release formulation still significantly impaired driving performance. The increase in SDLP from placebo after administration of alprazolam XR 1 mg was +3.9 cm, indicating effects well above those of alcohol while BACs are 0.5 mg/mL. A limitation of the study was that it was conducted with healthy, young volunteers. As is the case with insomnia patients, patients suffering from anxiety disorders may respond differently to the impairing effects of anxiolytics due to the underlying disorder and possible chronic use of anxiolytics. However, in contrast to the effects of hypnotics in insomnia patients, data already exist on the effects of anxiolytics in patients with anxiety disorders (O'Hanlon et al., 1995). Driving performance in anxiety patients appeared not to be different from that in healthy volunteers after both single and repeated doses of benzodiazepine anxiolytics. Moreover, it was shown that baseline and placebo performances were comparable between both groups. This suggests that the

results found in the study presented in *chapter 6* can be used for predicting effects of anxiolytics on driving in anxiety patients.

Conclusions

Studies presented in the previous chapters of this dissertation evaluated driving performance and driving related skills after administration of hypnotics and anxiolytics. One objective of this dissertation was to study whether the effects of hypnotics on driving performance found in previous research conducted with younger, healthy volunteers are predictive for the effects on performance of insomnia patients. Results showed that performance of the driving test after administration of hypnotics was not differentially affected by age or insomnia. It can, therefore, be concluded that studies investigating the residual effects of hypnotics on driving performance in young, healthy volunteers validly predict the effects of hypnotics in elderly and insomnia patients. In addition, effects of hypnotics do not appear to be different between females and males, indicating that there is no need to make a distinction in type of warning of the impairing effects of hypnotics.

Lastly, the effects of an extended release formulation of a benzodiazepine anxiolytic on highway driving appeared to be significantly reduced when compared to its immediate release equivalent. Yet, it may be concluded that the sedative effects of the extended release version were still of significant magnitude, resulting in an increased risk of becoming involved in a car accident.

REFERENCES

- Akerstedt, T., Fredlund, P., Gillberg, M. & Jansson, B. A prospective study of fatal occupational accidents -- relationship to sleeping difficulties and occupational factors. *J Sleep Res*, 2002, 11: 69-71.
- Alvarez, F. J. & Fierro, I. Older drivers, medical condition, medical impairment and crash risk. *Acc Anal Prev*, 2008, 40: 55-60.
- Ashton, H. The diagnosis and management of benzodiazepine dependence. *Curr Opin Psychiat*, 2005, 18: 249-255.

- American Psychiatric Association. *DSM-IV: Diagnostic and Statistical Manual of Mental Disorders*, Washington DC, American Psychiatric Press, 1994.
- Bastien, C. H., Leblanc, M., Carrier, J. & Morin, C. M. Sleep EEG power spectra, insomnia, and chronic use of benzodiazepines. *Sleep*, 2003, 26: 313-317.
- Bonnet, M. H. & Arand, D. L. 24-hour metabolic rate in insomniacs and matched normal sleepers. *Sleep*, 1995, 18: 581-588.
- Bonnet, M. H. & Arand, D. L. The consequences of a week of insomnia. *Sleep*, 1996, 19: 453-461.
- Bonnet, M. H. & Arand, D. L. Hyperarousal and insomnia. *Sleep Med Rev*, 1997, 1: 97-108.
- Busto, U. E., Kaplan, H. L., Wright, C. E., Gomez Mancilla, B., Zawertailo, L., Greenblatt, D. J. & Sellers, E. M. A comparative pharmacokinetic and dynamic evaluation of alprazolam sustained-release, bromazepam, and lorazepam. *J Clin Psychopharmacol*, 2000, 20: 628-635.
- Carskadon, M.A., Dement, W.C., Mitler, M.M., Guilleminault, C., Zarcone, V.P. & Spiegel, R. Self-reports versus sleep laboratory findings in 122 drug-free subjects with complaints of chronic insomnia. *Am J Psychiat*, 1976, 133: 1382-1388.
- Curran, H. V., Collins, R., Fletcher, S., Kee, S. C., Woods, B. & Iliffe, S. Older adults and withdrawal from benzodiazepine hypnotics in general practice: effects on cognitive function, sleep, mood and quality of life. *Psychol Med*, 2003, 33: 1223-1237.
- Drake, C. L., Roehrs, T. & Roth, T. Insomnia causes, consequences, and therapeutics: an overview. *Depress Anxiet*, 2003, 18: 163-176.
- Drummond, S. P. A., Smith, M. T., Orff, H. J., Chengazi, V. & Perlis, M. L. Functional imaging of the sleeping brain: review of findings and implications for the study of insomnia. *Sleep Med Rev*, 2004, 8: 227-242.
- Espie, C. A. Insomnia: conceptual issues in the development, persistence, and treatment of sleep disorder in adults. *Ann Rev Psychol*, 2002, 53: 215-243.

CHAPTER 7

- Fulda, S. & Schulz, H. Cognitive dysfunction in sleep disorders. *Sleep Med Rev*, 2001, 5: 423-445.
- ICADTS. Guidelines on experimental studies undertaken to determine a medicinal drug's effect on driving or skills related to driving. Cologne, Bundes Anstalt fuer Strassenwesen (BASt), 1999.
- Kamel, N. S. & Gammack, J. K. Insomnia in the elderly: cause, approach, and treatment. *Am J Med*, 2006, 119: 463-469.
- Langford, J., Methorst, R. & Hakamies-Blomqvist, L. Older drivers do not have a high crash risk - A replication of low mileage bias. *Acc Anal Prev*, 2006, 38: 574-578.
- Mumford, G. K., Evans, S. M., Fleishaker, J. C. & Griffiths, R. R. Alprazolam absorption kinetics affects abuse liability. *Clin Pharmacol Ther*, 1995, 57: 356-365.
- Neutel, I. Benzodiazepine-related traffic accidents in young and elderly drivers. *Hum Psychopharmacol Clin Exp*, 1998, 13: S115-S123.
- O'Hanlon, J. F., Vermeeren, A., Uiterwijk, M. M., Van Veggel, L. M. & Swijgman, H. F. Anxiolytics' effects on the actual driving performance of patients and healthy volunteers in a standardized test. An integration of three studies. *Neuropsychobiol*, 1995, 31: 81-88.
- O'Hanlon, J. F. & Volkerts, E. R. Hypnotics and actual driving performance. *Acta Psychiatr Scand. Supplementum*, 1986, 332: 95-104.
- Orff, H. J., Drummond, S. P. A., Nowakowski, S. & Perlis, M. L. Discrepancy between subjective symptomatology and objective neuropsychological performance in insomnia. *Sleep*, 2007, 30: 1205-1211.
- Paterniti, S., Dufouil, C. & Alperovitch, A. Long-term benzodiazepine use and cognitive decline in the elderly: the Epidemiology of Vascular Aging Study. *J Clin Psychopharmacol*, 2002, 22: 285-293.
- Perlis, M. L., Merica, H., Smith, M. T. & Giles, D. E. Beta EEG activity and insomnia. *Sleep Med Rev*, 2001a, 5: 365-376.
- Perlis, M. L., Smith, M. T., Andrews, P. J., Orff, H. J. & Giles, D. E. Beta/Gamma EEG activity in patients with primary and secondary insomnia and good sleeper controls. *Sleep*, 2001b, 24: 110-117.

- Pilcher, J. J. & Huffcutt, A. I. Effects of sleep deprivation on performance: a meta-analysis. *Sleep*, 1996, 19: 318-326.
- Rickels, K. Alprazolam extended-release in panic disorder. *Exp Opin Pharmacother*, 2004, 5: 1599-1611.
- Riedel, B. W. & Lichstein, K. L. Insomnia and daytime functioning. *Sleep Med Rev*, 2000, 4: 277-298.
- Sagberg, F. Driver health and crash involvement: a case-control study. *Acc Anal Prev*, 2006, 38: 28-34.
- Sagberg, F. & Bjornskau, T. Hazard perception and driving experience among novice drivers. *Acc Anal Prev*, 2006, 38: 407-414.
- Sgadari, A., Lapane, K. L., Mor, V., Landi, F., Bernabei, R. & Gambassi, G. Oxidative and nonoxidative benzodiazepines and the risk of femur fracture. The Systematic Assessment of Geriatric Drug Use Via Epidemiology Study Group. *J Clin Psychopharmacol*, 2000, 20: 234-239.
- Vermeeren, A., O'Hanlon, J. F., Declerck, A. C. & Kho, L. Acute effects of zolpidem and flunitrazepam on sleep, memory and driving performance, compared to those of partial sleep deprivation and placebo. *Acta Ther*, 1995, 21: 47-64.
- Vignola, A., Lamoureux, C., Bastien, C. H. & Morin, C. M. Effects of chronic insomnia and use of benzodiazepines on daytime performance in older adults. *J Gerontol*, 2000, 55: 54-62.
- Woodward, M. Hypnosedatives in the elderly. *CNS Drugs*, 1999, 11: 263-279.

CHAPTER 7

SUMMARY

SUMMARY

SUMMARY

One of the risk factors influencing crash involvement is the use of medicinal drugs and in particular the so-called 'psychoactive drugs'. Psychoactive medicinal drugs act primarily on the central nervous system and are widely used for the treatment of a variety of psychiatric and neurological problems. Among the most frequently prescribed psychoactive medicinal drugs are GABAergic hypnotics and anxiolytics, for the treatment of insomnia and anxiety disorders, respectively. Besides therapeutic effects, hypnotics and anxiolytics often produce side-effects or residual effects. They impair cognitive and psychomotor functions and negatively affect performance in a variety of tasks, such as driving.

To date, the impairing effects on driving of hypnotics and anxiolytics have been widely established in a large number of experimental studies mainly conducted with healthy young volunteers. Despite the vast amount of existing data concerning the effects of hypnotics and anxiolytics on driving, a number of questions still have remain unanswered. It is still not clear whether the results of experimental studies conducted with healthy young volunteers translate to therapeutic use in patients. Furthermore, it has not yet been clarified if residual effects of hypnotics are manifested differently between female and male users. To conclude, it has not been studied what the influence of change in formulation has on the adverse effects of an anxiolytic on driving performance.

Therefore, the aim of this dissertation is to evaluate to what extent the effects of hypnotics and anxiolytics on driving performance are modulated by factors, such as age, gender, disorder or drug formulation.

Chapter 1 - The study described in this chapter assessed the residual effects of evening and middle-of-night administration of gaboxadol 15 mg, evening administration of zopiclone 7.5 mg and middle-of-the-night administration of zolpidem 10mg, on cognitive, psychomotor and driving performance in healthy young volunteers.

A total of 25 young volunteers (12 women; mean age 31.4 years) completed a double-blind, placebo-controlled, active-referenced five-way cross over study. Each treatment night subjects ingested one capsule at 23:00 hours and one at 04:00 hours. Treatments were placebo at both times, gaboxadol 15 mg or zopiclone 7.5 mg followed by placebo, and placebo followed by gaboxadol 15 mg or zolpidem 10 mg. Effects on cognition and psychomotor performance were assessed between 07:30-08:30 hours, and on driving between 09:00-10:00 hours.

Driving performance after evening administration of gaboxadol 15 mg was not significantly impaired. Evening administration of zopiclone 7.5 mg and middle-of-the-night administration of gaboxadol 15 mg and zolpidem 10 mg resulted in significantly impaired driving performance. Evening administration of gaboxadol had minor effects on divided attention only, whereas middle-of-the-night administration significantly impaired performance in all tests except memory. Zolpidem and zopiclone significantly impaired performance in every test except tracking after zopiclone. Gaboxadol 15 mg can produce minor residual effects on driving after evening administration. Administration later at night is associated with moderately impairing residual effects on driving and psychomotor performance, but not on memory.

Chapter 2 - A limitation of the study described in the former chapter was that residual effects were established in younger drivers. The majority of users of hypnotics are older people, however, who may be more sensitive to drug effects. The aim of this study was to evaluate the residual effects the morning after evening doses of temazepam 20 mg and zopiclone 7.5 mg on driving performance in healthy elderly drivers.

Eighteen healthy elderly drivers (10 female and 8 male; mean age 64.3 years) participated in a double-blind, three-way crossover study. Treatments were single oral doses of temazepam 20 mg, zopiclone 7.5 mg and placebo administered at bedtime. Subjects performed a standardized highway driving test between 10 and 11 hours after hypnotic intake. Before and after the driving test cognitive performance was assessed.

SUMMARY

Driving performance did not differ between temazepam and placebo, but was significantly impaired following zopiclone 7.5 mg ($p < 0.002$). The results of the laboratory tests were in line with the effects on driving of both hypnotics.

It was concluded that temazepam 20 mg is unlikely to impair driving 10 hours or more after bedtime administration in healthy elderly aged 75 years or younger. Zopiclone 7.5 mg moderately impairs driving in elderly at least until 11 hours after administration. The magnitude of impairing effects in elderly was comparable to those found previously in younger volunteers.

Chapter 3 - In many European countries, Canada and Japan, the non-benzodiazepine zopiclone now is among the most frequently prescribed hypnotic drugs. This can be explained by the growing view among physicians that zopiclone is more effective and safer than conventional benzodiazepines. It has been shown, however, in four studies using similar procedures that zopiclone 7.5 mg produces moderate to severe impairment on driving performance. The study described in this chapter aimed to review these studies and analyze the pooled data to determine whether the severity of effects is modified by the gender and age of the subjects.

Results showed that zopiclone 7.5 mg has significant and clinically relevant impairing effects on driving performance in the morning, until 11 hours after bedtime ingestion. The effects did not differ between males and females and did not increase with age, at least until 75 years.

It was concluded that patients using an evening dose of zopiclone 7.5 mg should avoid activity in skilled work and participation in traffic the morning after intake. General practitioners' beliefs about the beneficial safety profile of zopiclone may need adjustment and patients using zopiclone 7.5 mg should be warned accordingly. In addition, there is no need to differentiate warnings about zopiclone's residual impairing effects depending on the gender of the patient.

Chapter 4 - It has not yet been clarified to what extent actual driving performance is affected by insomnia. In addition, it remains to be determined whether chronic use of hypnotics has deteriorating effects on driving

performance in patients suffering from insomnia. Therefore, the aim of the present study was to explore the effects of insomnia and chronic use of hypnotics on driving in a one hour standardized driving test in actual traffic.

A total of 22 elderly insomnia patients chronically using hypnotics, 20 elderly insomniacs infrequently or not using hypnotics and 21 healthy, age-matched controls performed a standardized highway driving test between 10 and 11 hours after bedtime. Before the driving test cognitive performance was assessed.

Results indicate that driving performance is not impaired in patients suffering from insomnia, irrespective of use of hypnotics. In addition, driving related psychomotor and cognitive performance appeared not to be affected in medicated and unmedicated insomnia patients.

Insomnia patients appear to be able to successfully perform a one hour driving task that requires prolonged attentional demands. Chronic use of hypnotic does not seem to change driving performance.

Chapter 5 - As mentioned in the previous chapters, residual effects of hypnotics on actual driving performance have been mainly determined in studies using a standardized driving test with healthy good sleepers. Responses to these effects may differ, however, between insomniacs and healthy volunteers due to the underlying sleep disorder. Performance in insomniacs is expected to improve due to the sleep improving effects of hypnotics and may attenuate the impairing effects. In addition, a majority of insomniacs uses hypnotics chronically resulting in the development of tolerance to impairing effects. Impaired driving performance in healthy volunteers may then be an overestimation of the actual effects in insomniacs.

The study described in this chapter aimed to compare the residual effects of the frequently prescribed hypnotic zopiclone 7.5 mg on driving performance of 16 elderly insomniacs chronically using hypnotics (frequent users), 16 elderly insomniacs not or infrequently using hypnotics (infrequent users) and 16 healthy, age matched, good sleepers (controls).

SUMMARY

The study was conducted according to a 3x2 double-blind, placebo controlled crossover design, with three groups and two treatment conditions. Treatments were single oral doses of zopiclone 7.5 mg and placebo administered immediately before retiring to bed at 23:30 hours. Between 10 and 11 hours after administration subjects performed a standardized highway driving test.

Results indicated that zopiclone 7.5 mg significantly impaired driving performance in both insomnia groups and healthy controls. The magnitude of impairment was, however, significantly less in the frequent users group as compared with the controls. Effects found in the infrequent users were in line with previous studies, suggesting that these studies are able to validly predict the residual effects of hypnotics in insomnia patients who do not or infrequently use hypnotics. Chronic use of hypnotics seems to attenuate the severity of effects of zopiclone 7.5 mg. Nevertheless, this reduction does not result in an absence of impairing effects in insomnia patients chronically using hypnotics.

Chapter 6 - Alprazolam extended-release (XR) is approved for the treatment of panic disorder. This sustained formulation is absorbed in a delayed manner and is therefore expected to produce fewer and less severe side effects than its immediate release equivalent (alprazolam IR). The effect of alprazolam XR on potentially dangerous daily activities, such as driving a car, is expected to be less as compared to alprazolam IR.

The study presented in this chapter was designed to compare the effects of alprazolam XR (1 mg) and alprazolam IR (1 mg) on actual driving ability and cognitive function.

Eighteen healthy volunteers (aged 20-45 years) participated in a double blind, placebo-controlled, three-way crossover study. At 4 hours post dose, subjects performed a standardized driving test on a primary highway in normal traffic. Cognitive and psychomotor tests were assessed 1, 2.5 and 5.5 hours post dose. Memory functioning was measured only 1 hour after administration.

Results showed that both formulations severely impaired driving performance between 4 and 5 hours after administration. The magnitude of

impairment in the driving test observed with alprazolam XR was about half that observed with alprazolam IR. Laboratory test results were in line with the driving data.

It was concluded that the acute impairing effects of alprazolam XR 1 mg on driving and psychomotor functions were generally less as compared to its immediate release equivalent, but still of sufficient magnitude to increase the risk of becoming involved in traffic accidents.

Chapter 7 - This chapter summarizes and discusses the results from the studies described in the previous chapters. Results showed that performance of the driving test after administration of hypnotics was not differentially affected by age, gender or insomnia. It was therefore concluded that studies investigating the residual effects of hypnotics on driving performance in young, healthy volunteers validly predict the effects of hypnotics in elderly, insomnia patients.

Lastly, the effects of an extended release formulation of a benzodiazepine anxiolytic on highway driving appeared to be significantly reduced when compared to its immediate release equivalent. Yet, it was concluded that the sedative effects of the extended release version were still of significant magnitude, resulting in an increased risk of becoming involved in a car accident.

SUMMARY

SAMENVATTING

SAMENVATTING

Eén van de risicofactoren die de betrokkenheid bij een verkeersongeval beïnvloeden is het gebruik van medicijnen, en daarbij in het bijzonder de zogenaamde 'psychoactieve medicijnen'. Psychoactieve medicijnen werken primair op het centrale zenuwstelsel en worden veelvuldig gebruikt voor de behandeling van een verscheidenheid van psychiatrische en neurologische problemen. Een frequent voorgeschreven groep psychoactieve medicijnen is de groep van de GABAerge hypnotica en anxiolytica. GABAerge hypnotica en anxiolytica worden voorgeschreven voor de behandeling van, respectievelijk, slaap- en angststoornissen. Naast therapeutische effecten produceren deze medicijnen echter ook bijwerkingen of residueffecten. Ze verslechteren cognitieve en psychomotore functies en beïnvloeden daardoor de prestatie in activiteiten, zoals autorijden.

De effecten van hypnotica en anxiolytica op de rijvaardigheid zijn de laatste jaren uitgebreid onderzocht in een groot aantal experimentele studies. De proefpersonen in deze studies waren voornamelijk jonge, gezonde vrijwilligers. Hoewel deze studies relevante data hebben opgeleverd over de effecten van hypnotica en anxiolytica, zijn er nog een aantal vragen onbeantwoord gebleven. Het is bijvoorbeeld nog niet duidelijk of the resultaten van de experimentele studies met jonge vrijwilligers vertaald kunnen worden naar effecten bij therapeutisch gebruik door patiënten. Verder is er nog geen antwoord gevonden op de vraag of de residueffecten verschillend tot uiting komen bij vrouwelijke en mannelijke gebruikers. Tot slot is er nog geen onderzoek gedaan naar de invloed van een verandering in formulering van een anxiolyticum op de rijvaardigheid.

Het doel van dit proefschrift is daarom om na te gaan in hoeverre the effecten van hypnotica en anxiolytica op de rijprestatie worden gemoduleerd door factoren, zoals leeftijd, geslacht, stoornis of formulering van het middel.

Hoofdstuk 1 - In de studie die beschreven is in dit hoofdstuk zijn de residueffecten onderzocht na inname van avond- en nachtdoseringen van

gaboxadol 15 mg, avonddosering van zopiclon 7.5 mg en nachtdosering van zolpidem 10 mg op cognitie, psychomotore functies en rijvaardigheid van gezonde, jonge vrijwilligers.

In totaal deden 25 jonge vrijwilligers (12 vrouwen en 13 mannen; gemiddelde leeftijd 31.4 jaar) mee aan een dubbelblind, placebogecontroleerd, vijf-wegs, gekruist onderzoek. In iedere behandelingsconditie namen de proefpersonen één capsule in om 23:00 uur en één om 04:00 uur. De capsules bevatten placebo op beide tijdstippen, gaboxadol 15 mg of zopiclon 7.5 mg gevolgd door placebo, en placebo gevolgd door gaboxadol 15 mg of zolpidem 10 mg. De effecten op cognitie en psychomotore functies werden gemeten tussen 07:30 en 08:30 uur en de effecten op de rijvaardigheid tussen 09:00 en 10:00 uur.

Na avonddinname van gaboxadol 15 mg bleek de rijvaardigheid niet significant verslechterd te zijn. Avonddinname van zopiclon 7.5 mg en nachtdinname van gaboxadol 15 mg en zolpidem 10 mg resulteerde wel in een significante achteruitgang in de rijvaardigheid. Avonddinname van gaboxadol produceerde alleen lichte effecten op verdeelde aandacht, maar de nachtdinname van gaboxadol verslechterde de prestatie significant in alle testen behalve de geheugentest. Prestaties in alle cognitieve en psychomotore taken waren significant verslechterd na inname van zolpidem en zopiclon, met uitzondering van de zogenaamde 'tracking' taak. Gaboxadol 15 mg veroorzaakt milde residueffecten op rijvaardigheid na avonddinname. Nachtdinname van gaboxadol veroorzaakt matige residueffecten op rijvaardigheid en psychomotore functies, maar niet op geheugen.

Hoofdstuk 2 - Een beperking van het onderzoek dat beschreven staat in het vorige hoofdstuk was dat de residueffecten werden onderzocht bij jonge automobilisten. De meerderheid van hypnoticagebruikers is echter ouder dan 45 jaar en kan gevoeliger zijn voor de bijwerkingen van geneesmiddelen. Het doel van het onderzoek beschreven in dit hoofdstuk was dan ook om na te gaan wat de residueffecten op de rijprestatie zijn in de ochtend na avonddinname van temazepam 20 mg en zopiclon 7.5 mg in gezonde, oudere automobilisten.

SAMENVATTING

Achttien gezonde, oudere vrijwilligers (10 vrouwelijk en 8 mannelijk; gemiddelde leeftijd 64.3 jaar) namen deel aan een dubbelblind, drie-wegs, gekruist onderzoek. De behandelingen waren eenmalige doseringen van temazepam 20 mg, zopiclon 7.5 mg en placebo ingenomen vóór het slapen. Tussen 10 en 11 uur na inname voerden de proefpersonen een gestandaardiseerde rijtest uit op de autosnelweg. Voorafgaand en na de rijtest werden hun cognitieve functies gemeten.

De rijvaardigheid verschildte niet tussen de temazepam en placebo conditie, maar was significant verslechterd na inname van zopiclon 7.5 mg ($p < 0.002$). De resultaten van de cognitieve testen waren vergelijkbaar met de effecten die gevonden waren in de rijtest.

Geconcludeerd werd dat het onwaarschijnlijk is dat de rijvaardigheid bij gezonde oudere rijders verslechterd is 10 uur of langer na inname van temazepam 20 mg. De rijvaardigheid van oudere automobilisten wordt wel significant verslechterd tot 11 uur na inname van zopiclon 7.5 mg. De mate van de verslechtering bij ouderen was vergelijkbaar met die bij jongeren, zoals gemeten in vorig onderzoek.

Hoofdstuk 3 - In een groot aantal Europese landen, Canada en Japan is zopiclon één van de meest voorgeschreven slaapmiddelen. Dit is waarschijnlijk te wijten aan het feit dat artsen van mening zijn dat zopiclon effectiever en veiliger is dan de conventionele benzodiazepines. Echter, vier studies, waarin gebruik gemaakt werd van vergelijkbare procedures, hebben aangetoond dat zopiclon 7.5 mg de rijvaardigheid matig tot ernstig kan verslechteren. Het onderzoek dat beschreven staat in dit hoofdstuk had als doel een overzicht te geven van deze studies en om de data daarvan samen te voegen om te kunnen bepalen of de ernst van de effecten varieert met leeftijd en geslacht.

De resultaten toonden aan dat zopiclon 7.5 mg significante en klinisch relevante verslechterende effecten heeft op de rijvaardigheid 's ochtends tot 11 uur na avondinname. De effecten bleken niet te verschillen tussen mannen en vrouwen en waren niet groter naarmate de leeftijd toeneemt, tenminste tot 75 jaar.

Geconcludeerd werd dat patiënten die 's avonds zopiclon 7.5 mg innemen, 's ochtends niet zouden moeten deelnemen aan het verkeer. De mening van artsen ten aanzien van de effecten van zopiclon verdient bijstelling in zoverre dat patiënten dienen te worden geadviseerd en gewaarschuwd over de residueffecten van het gebruik van zopiclon 7.5 mg op rijvaardigheid. De adviezen en waarschuwingen gelden in gelijke mate voor mannen en vrouwen.

Hoofdstuk 4 - Het is nog niet onderzocht in welke mate rijvaardigheid wordt beïnvloed door insomnie. Daarnaast is het nog niet duidelijk of chronisch gebruik van slaapmiddelen negatieve effecten heeft op rijvaardigheid van insomniepatiënten. Het doel van het onderzoek dat beschreven staat in dit hoofdstuk was om de effecten van insomnie en chronisch gebruik van hypnotica op rijvaardigheid te onderzoeken met een gestandaardiseerde rijtest.

In totaal voerden 22 oudere insomniepatiënten die chronisch slaapmiddelen gebruiken, 20 oudere insomniepatiënten die niet of nauwelijks slaapmiddelen gebruiken, en 21 gezonde, leeftijdsgecontroleerde controle proefpersonen, een gestandaardiseerde rijtest uit op de autosnelweg tussen 10 en 11 uur na bedtijd uit. Voorafgaand aan de rijtest werden de cognitieve functies gemeten.

De resultaten lieten zien dat de rijvaardigheid niet verslechterd was bij patiënten met insomnie, ongeacht het gebruik van hypnotica. Bovendien bleek ook de prestatie in testen van psychomotoire en cognitieve functies niet anders te zijn in beide insomniegroepen in vergelijking met controles.

Insomniepatiënten blijken de één uur durende rijtest adequaat te kunnen uitvoeren. Rijvaardigheid, zoals gemeten met deze test, bleek niet te veranderen bij chronisch gebruik van slaapmiddelen.

Hoofdstuk 5 - Zoals blijkt uit de vorige hoofdstukken zijn de residueffecten van hypnotica op de rijvaardigheid voornamelijk onderzocht in gezonde, goede slapers. De onderliggende slaapstoornis bij insomniepatiënten zou er echter voor kunnen zorgen dat de veranderingen in gedrag ten gevolge van de residueffecten kan verschillen tussen patiënten en gezonde vrijwilligers. Verwacht kan worden dat de prestatie verbetert bij insomniepatiënten door de

SAMENVATTING

therapeutische effecten van hypnotica op de slaap en dat daardoor de verslechterende effecten, zoals ze zijn gevonden in gezonde vrijwilligers, afgezwakt worden. Verder gebruikt de meerderheid van de insomniepatiënten hypnotica op een chronische manier, wat kan resulteren in de ontwikkeling van tolerantie voor de verslechterende effecten van hypnotica. De gevonden achteruitgang in rijvaardigheid in gezonde vrijwilligers zou dan een overschatting kunnen zijn van de werkelijke effecten bij insomniepatiënten.

Het onderzoek dat beschreven staat in dit hoofdstuk had als doel om de residueffecten van het frequent voorgeschreven hypnoticum zopiclon 7.5 mg op rijvaardigheid te vergelijken tussen 16 oudere insomniepatiënten die chronisch hypnotica gebruiken (frequente gebruikers), 16 oudere insomniepatiënten die niet of nauwelijks hypnotica gebruiken (infrequente gebruikers), en 16 gezonde, goede slapers van dezelfde leeftijd (controles).

Het onderzoek werd uitgevoerd volgens een 3x2 dubbelblind, placebogecontroleerd, gekruist design. De behandelingen waren eenmalige doseringen van zopiclon 7.5 mg en placebo ingenomen direct voorafgaand aan het slapen om 23:30 uur. Tussen 10 en 11 uur na inname voerden de proefpersonen een gestandaardiseerde rijtest uit op de autosnelweg.

De resultaten lieten zien dat zopiclon 7.5 mg de rijvaardigheid significant verslechterde in beide insomniegroepen en in de gezonde controle groep. De mate van verslechtering was echter significant kleiner in de frequente gebruikers groep vergeleken met de controle groep. De effecten die gevonden werden in de infrequente gebruikers waren vergelijkbaar met de effecten gevonden in gezonde vrijwilligers van vorige onderzoeken. Het lijkt dat de residueffecten van hypnotica gemeten in studies met gezonde vrijwilligers een valide afspiegeling zijn van de effecten in insomniepatiënten die niet of nauwelijks hypnotica gebruiken. Chronisch gebruik van hypnotica lijkt de ernst van effecten af te zwakken. Echter, deze vermindering resulteerde niet in een afwezigheid van de verslechterende effecten van zopiclon 7.5 mg in insomniepatiënten die chronisch hypnotica gebruiken en kan beïnvloed zijn door ontwenningverschijnselen in de placeboconditie.

Hoofdstuk 6 - Alprazolam extended-release (XR) wordt voorgeschreven voor de behandeling van paniekstoornissen. De formulering van het middel zorgt voor een vertraagde afgifte en opname en veroorzaakt daardoor mogelijk minder frequente en minder ernstige bijwerkingen dan de directe afgifte formulering (alprazolam immediate release; IR). Het effect van alprazolam XR op mogelijk risicovolle dagelijkse activiteiten, zoals autorijden, zou dan ook minder ernstig kunnen zijn dan alprazolam IR.

Het onderzoek dat gepresenteerd wordt in dit hoofdstuk was opgezet om de effecten van alprazolam XR (1 mg) en alprazolam IR (1 mg) op rijvaardigheid en cognitief functioneren te vergelijken.

Achttien gezonde vrijwilligers (tussen 21 en 45 jaar oud) namen deel aan een dubbelblind, placebogecontroleerd, drie-wegs, gekruist onderzoek. Vier uur na inname voerden de proefpersonen een gestandaardiseerde rijtest uit op de autosnelweg. De effecten op cognitie en psychomotore functies werden gemeten op 1, 2.5 en 5.5 uur na inname. Een verbale geheugentest werd alleen 1 uur na inname afgenomen.

De resultaten toonden aan dat beide formuleringen de rijvaardigheid ernstig verslechterde tussen 4 en 5 uur na inname. De mate van achteruitgang in de rijtest na inname van alprazolam XR was ongeveer de helft van dat na inname van alprazolam IR. De resultaten van de laboratoriumtesten waren vergelijkbaar met de resultaten van de rijtest.

Geconcludeerd werd dat de acute verslechterende effecten van alprazolam XR 1 mg op rijvaardigheid en psychomotore functies over het algemeen kleiner waren dan van alprazolam IR 1 mg. Echter, de mate van achteruitgang was nog steeds van dien aard dat de kans betrokken te raken bij een verkeersongeluk verhoogd is.

Hoofdstuk 7 - In dit hoofdstuk worden de resultaten van de onderzoeken die beschreven staan in de vorige hoofdstukken samengevat en besproken. De resultaten toonden aan dat de prestatie op de rijtest na inname van hypnotica niet verschillend beïnvloed werd door leeftijd, geslacht of insomnie. Geconcludeerd werd daarom dat studies waarin de residueffecten van

SAMENVATTING

hypnotica op rijvaardigheid worden onderzocht in jonge, gezonde vrijwilligers, de effecten op een valide manier kunnen voorspellen in oudere, insomniepatiënten.

Tot slot, de effecten op rijvaardigheid van een anxiolyticum met een vertraagde afgifte formulering bleken significant te zijn afgenomen vergeleken met de directe afgifte formulering. Echter, geconcludeerd werd dat de sedatieve effecten van de vertraagde afgifte formulering nog steeds van dien aard waren dat gebruik van het middel de kans betrokken te raken bij een auto-ongeluk verhoogd.

DANKWOORD

DANKWOORD

DANKWOORD

Het uitvoeren van een onderzoek is (gelukkig) geen éénmansactie. De voltooiing van dit proefschrift heb ik dan ook te danken aan de begeleiding en steun van vele anderen.

Allereerst wil ik mijn copromotor Annemiek Vermeeren bedanken. Annemiek, hartelijk dank voor de afgelopen vier jaar. Ik heb zo ontzettend veel van je geleerd. Je hebt me geïntroduceerd in de fascinerende wereld van de psychofarmaca en de slaap. Bedankt voor de inspirerende ideeën, de vele adviezen en de vrijheid die je me hebt gegeven in mijn onderzoek- en onderwijsactiviteiten. Ik ben blij dat we onze samenwerking de komende twee jaar nog kunnen voortzetten.

Veel dank ook aan mijn promotor Wim Riedel. Bedankt voor de wijze woorden op afstand en de vaak, zo ogenschijnlijk, simpele adviezen en oplossingen tijdens de verschillende studies. Ik heb het ook altijd erg gewaardeerd dat we behalve onderzoek ook over onze andere gedeelde passie konden praten.

Jan Ramaekers wil ik bedanken voor de kans die ik kreeg om te komen werken bij de Experimentele Psychofarmacologie Unit (EPU). Bedankt ook voor je commentaar op een aantal hoofdstukken in dit proefschrift en de prettige gesprekken over een wetenschappelijke carrière.

Aan de praktische uitvoering van de verschillende onderzoeken die beschreven staan in dit proefschrift heeft een groot aantal mensen meegeholpen. De rij-instructeurs, Henk Brauers, Willy Jeurissen, Jo Gorissen en Hans Sleebe hebben voor de veiligheid gezorgd van de proefpersonen tijdens de rijtest op de autosnelweg. Heel veel dank voor jullie inzet tijdens al die tienduizenden kilometers. Irma Brauers wil ik bedanken voor alle logistieke werkzaamheden rondom de rijtest, voor alle 'rondjes Limburg', voor de verwerking van honderden rijschema's, en het stimuleren van de proefpersonen en patiënten tijdens hun deelname. Cees van Leeuwen dank ik voor de vele medische keuringen van de proefpersonen en de vrijwel continue beschikbaarheid voor medische vragen over de deelnemers. Anita van Oers

bedank ik voor de assistentie in alle studies. Dank ook voor je collegialiteit en het feit dat je me vrijwel altijd meteen hielp bij problemen met het analyseren van de ritten. Al de Weerd en Renilde van den Bossche van SEIN, Zwolle, dank ik voor de vele analyses van de slaapregistraties tijdens de laatste twee studies. Student-assistenten en stagiaires, Janneke Guyaux, Roland Otten, Wei Lie Woo, Samantha Irwin, Elmy Theuniszen, Jolien Gooijers, Floor van de Water, Liene Ketelslegers, Tim Weysen, Jasmijn Kromhout, Loes van Langen, Gwenda Engels, Natalie Valle Guzman en Nicky van Gennip, heel veel dank voor jullie hulp en enthousiasme. Heren van de instrumentatie, bedankt voor de reparaties en controles van alle testapparatuur. Heren van de ICT, dank voor de ondersteuning bij alle hard- en software vraagstukken. Alle proefpersonen, bedankt voor jullie deelname en de interesse in het onderzoek.

Mijn collega's en ex-collega's wil ik bedanken voor de prettige werksfeer op de tweede verdieping. In het bijzonder noem ik Kim Kuypers, Marleen Wingen en Eef Theunissen voor alle adviserende, serieuze, blijde, boze, bizarre, opbeurende en inspirerende gesprekken. Verder dank ik Elian Stassen, Jeroen van Deursen, Wendy Bosker, Anke Sambeth, Eric Vuurman, Petra Hurks, Pascal van Gerven, Sven Stapert, Rob Markus, Christine Firk en alle anderen. Arie van der Lugt, Alard Roebroek, Michael Capalbo en Jos Prickaerts bedank ik voor de steun en het vertrouwen dat jullie mij hebben gegeven op het gebied van onderwijs. Arjan Blokland dank ik voor de samenwerking in de 'andere' onderzoeksstages en de vele informatieve gesprekken. Harm Hospers, bedankt voor je luisterend oor, je advies en interesse.

Peter van Ruitenbeek en Silke Conen, mijn kamergenoten, bedankt voor jullie bijdrage aan een geweldige sfeer op onze kamer. Bedankt voor de fijne samenwerking.

Mijn paranimfen, mijn vrienden, Danny Lebioda en Mischa Coenen, bedankt voor jullie vriendschap en jullie oprechte interesse in mijn leven. Ik vind het een eer dat jullie me bij willen staan tijdens mijn promotie.

Yves Dupuits en Paul Kerkhoffs, bedankt voor jullie muziek, onbegrensde ideeën en het samen strijden tegen de schaarsheid der bezieling. Yves en ook

DANKWOORD

Sanne Stockbroekx, bedankt voor het fantastische ontwerp van de omslag van dit proefschrift.

Mijn lieve familie, Dennis, Simone en Evi Leufkens, bedankt voor jullie interesse in mijn onderzoek en voor het feit dat jullie deur altijd open staat. Dennis, bedankt voor je energie en de mooie fietstochten. Oma, bedankt voor uw steun en alle zorg die u mij heeft gegeven.

Jos en Ria Leufkens, pap en mam, jullie wil ik ontzettend bedanken voor het feit dat jullie er simpelweg altijd zijn. Jullie hebben me de vrijheid gegeven om mijn eigen pad te kiezen en steunen me daarin onvoorwaardelijk. Mijn dank is groot voor jullie vertrouwen in mij.

Slutligen skulle jag innerligt vilja tacka min älskade, Margit Vikström. Margit, du har stöttat mig villkorslöst. Tack så mycket för all din hjälp, din kärlek och din energi. Tack för att du gör livet intressant.

CURRICULUM VITAE

CURRICULUM VITAE

Tim Leufkens werd geboren op 17 maart 1978 te Berg aan de Maas. In 1996 behaalde hij het VWO diploma aan het College Sittard. Aansluitend begon hij met de opleiding tot operatieassistent aan de Hogeschool Limburg in Heerlen. Het praktijkgedeelte van deze studie voerde hij uit op de operatieafdeling van het Laurentius Ziekenhuis te Roermond. In 1999 rondde hij de studie af en was hij werkzaam als junior operatieassistent van maart 2000 tot september 2000 in hetzelfde ziekenhuis. In september 2000 begon hij met zijn studie Psychologie aan de Universiteit Maastricht, waarbij hij koos voor de afstudeerrichting Neuropsychologie. Hij studeerde af in 2004 na een onderzoeksstage bij de vakgroepen Neurocognitie (Faculteit der Psychologie) en Neurowetenschappen en Neurochirurgie (Faculteit der Geneeskunde), met als onderwerp impulsiviteit bij hoogfrequente bilaterale stimulatie van de nucleus subthalamicus bij de Ziekte van Parkinson. In 2005 was hij als onderzoeksmedewerker bij de vakgroep Neurocognitie betrokken bij een onderzoek van de Experimentele Psychopharmacology Unit onder leiding van Prof. dr. J.G. Ramaekers en Dr. A. Vermeeren. In datzelfde jaar begon hij met promotieonderzoek naar de effecten van slaap- en kalmeringsmedicatie op cognitieve functies en rijvaardigheid onder begeleiding van Prof. dr. W.J. Riedel en Dr. A. Vermeeren. Uiteindelijk heeft dit geresulteerd in het huidige proefschrift. Vanaf juni 2009 is Tim Leufkens werkzaam als post-doc onderzoeker bij de vakgroep Neuropsychologie en Psychofarmacologie, Faculteit der Psychologie en Neurowetenschappen aan de Universiteit Maastricht.

PUBLICATIONS

PUBLICATIONS

PUBLICATIONS

Journal article:

Leufkens TRM, Vermeeren A. (in press) Highway driving in elderly the morning after bedtime use of hypnotics: a comparison between temazepam 20 mg, zopiclone 7.5 mg and placebo. *Journal of Clinical Psychopharmacology*.

Leufkens TRM, Lund JS, Vermeeren A (in press) Highway driving performance and cognitive functioning the morning after bedtime and middle-of-the-night use of gaboxadol, zopiclone and zolpidem. *Journal of Sleep Research*.

Leufkens TRM, Vermeeren A, Smink BE, van Ruitenbeek P, Ramaekers JG (2007) Cognitive, psychomotor and actual driving performance in healthy volunteers after immediate and extended release formulations of alprazolam 1 mg, *Psychopharmacology*, 191, 951-959.

Leufkens TRM, Vermeeren A. (submitted) Zopiclone's residual effects on actual driving performance in a standardized test: A pooled analysis of age and gender effects in four placebo controlled studies.

Book contribution:

Verster JC, Mets MAJ, **Leufkens TRM**, Vermeeren A (2009) Insomnia, hypnotic drugs and traffic safety. In JC Verster, SR Pandi-Perumal, JG Ramaekers, JJ de Gier (Eds.), *Drugs, Driving and Traffic Safety* (pp. 233-244). Basel: Birkhäuser Verlag AG.

Vermeeren A, **Leufkens TRM**, Verster JC (2009) Effects of anxiolytics on driving. In JC Verster, SR Pandi-Perumal, JG Ramaekers, JJ de Gier (Eds.), *Drugs, Driving and Traffic Safety* (pp. 289-306). Basel: Birkhäuser Verlag AG.

Leufkens TRM, Van Leeuwen CJ, Van Oers A, Guijaux J, Woo W, Vermeeren A (2008) Residual effects of gaboxadol on highway driving and cognitive

performance of healthy volunteers. In GSF Ruigt, T de Boer, V van Kasteel, G van Luijtelaar, S Overeem (Eds.), *Sleep-Wake Research in The Netherlands, volume 19* (pp. 97-100). Enschede: PrintPartners Ipskamp BV.

Leufkens TRM, Guijaux J, Irwin SL, Vermeeren A (2008) Lack of age differences in residual effects of zopiclone 7.5 mg on memory, attention and psychomotor performance. In GSF Ruigt, T de Boer, V van Kasteel, G van Luijtelaar, S Overeem (Eds.), *Sleep-Wake Research in The Netherlands, volume 19* (pp. 101-103). Enschede: PrintPartners Ipskamp BV.

Leufkens TRM, Irwin SL, Guijaux, J, Vermeeren A (2007) Temazepam 20 mg improves sleep without residual effects in elderly drivers. In GSF Ruigt, T de Boer, V van Kasteel, G van Luijtelaar, S Overeem (Eds.), *Sleep-Wake Research in The Netherlands, volume 18* (pp. 87-92). Enschede: PrintPartners Ipskamp BV.

Abstract:

Leufkens TRM, van Ruitenbeek P, van Oers ACM, Guijaux J, Otten RWH, Vermeeren A, Ramaekers JG (2006) Cognitive, psychomotor and actual driving performance after immediate and extended release formulations of alprazolam 1 mg, *Journal of Psychopharmacology*, 20 (Suppl 5), A30.

PUBLICATIONS